NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/US02/17411, filed June 3, 2002, which claims priority from U.S. Provisional Application No. 60/295,301 filed on June 1, 2001; all of these applications incorporated herein by reference.

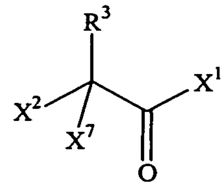
BACKGROUND OF THE INVENTION

This Application relates to compounds and compositions for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsin S.

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increase expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. An increase in cathepsin S activity contributes to the pathology and/or symptomatology of a number of diseases. Accordingly, molecules that inhibit the activity of cathepsin S protease are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHX^4$;

X^2 is hydrogen, fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH{=}CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^5 is hydrogen, (C_{1-4})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl; R^6 is hydrogen, hydroxy or (C_{1-6})alkyl; or where X^3 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl or hetero(C_{8-10})bicycloaryl; R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$; R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or (C_{5-10})heteroaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen, fluoro, -OH, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

wherein within R^5, X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene,

cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5, R^{12} and R^{13} are as defined above;

R^3 is (C_{1-6})alkyl or $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6})alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,

$-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5, R^{12}, R^{13} and R^{14} are as defined above;

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^8 is (C_{1-6})alkylene and X^5, R^{12}, R^{13} and R^{14} are as defined above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-3})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

R^{15} is (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl;

R^{17} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then R^{17} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

R^{18} is hydrogen, (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-6})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then R^{18} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl; and

wherein within R^3, R^4, R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$,

$-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any aromatic ring system present within R^{14} or R^{18} is not substituted further by halo, (C_{3-10})cycloalkyl, hetero(C_{3-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl; with the proviso that only one bicyclic ring structure is present within R^3, R^4 or R^{15}; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

A second aspect of the invention is a pharmaceutical composition which contains a compound of Formula I or their *N*-oxide derivatives, individual isomers or mixture of isomers thereof, or pharmaceutically acceptable salts thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

"Aliphatic" means a moiety characterized by a straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C_{6-10})aryl(C_{0-3})alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C_{1-6})alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$) 2-butenylene ($-CH_2CH{=}CHCH_2-$), 2-methyltetramethylene ($-CH_2CH(CH_3)CH_2CH_2-$), pentamethylene ($-CH_2CH_2CH_2CH_2CH_2-$) and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6})alkylidene includes methylidene ($=CH_2$), ethylidene ($=CHCH_3$), isopropylidene ($=C(CH_3)_2$), propylidene ($=CHCH_2CH_3$), allylidene ($=CH^{\cdot}CH{=}CH_2$), and the like).

"Amino" means the radical $-NH_2$. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting

groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to 4n+2.

"Aryl" means a monocyclic or fused bicyclic ring assembly containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly. For example, optionally substituted (C_{6-10})aryl as used in this Application includes, but is not limited to, biphenyl-2-yl, 2-bromophenyl, 2-bromocarbonylphenyl, 2-bromo-5-fluorophenyl, 4-*tert*-butylphenyl, 4-carbamoylphenyl, 4-carboxy-2-nitrophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorocarbonylphenyl, 4-chlorocarbonylphenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 4-chloro-2-nitrophenyl, 6-chloro-2-nitrophenyl, 2,6-dibromophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2-difluoromethoxyphenyl, 3,5-dimethylphenyl, 2-ethoxycarbonylphenyl, 2-fluorophenyl, 2-iodophenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 5-methyl-2-nitrophenyl, 4-methylsulfonylphenyl, naphth-2-yl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2,3,4,5,6-pentafluorophenyl, phenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylsulfanylphenyl, 4-trifluoromethylsulfanylphenyl, and the like. Optionally substituted (C_{6-10})aryl as used in this Application includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminomethylphenyl, biphenyl-4-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl, 3-phenoxyphenyl, phenyl, and the like.

"Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{9-10})bicycloaryl includes cyclohexylphenyl, 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl, and the like).

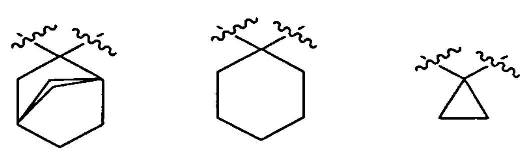
"Carbamoyl" means the radical $-C(O)NH_2$. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and protected derivatives fall within the scope of the invention.

"Carbocyclic ketone derivative" means a derivative containing the moiety –C(O)–.

"Carboxy" means the radical -C(O)OH. Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-10})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like).

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, the instance wherein "R^1 and R^2 together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene" includes, but is not limited to, the following:



"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

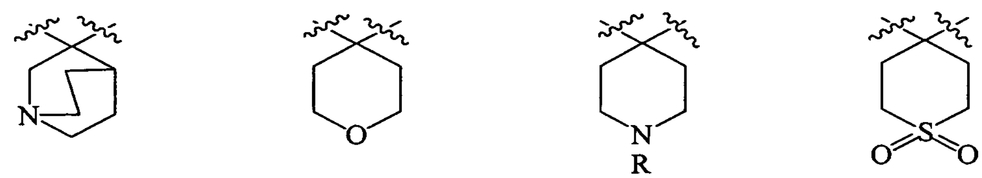
"Halo" means fluoro, chloro, bromo or iodo.

"Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like

(e.g. halo-substituted (C_{1-3})alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroatom moiety" includes -N=, -NR-, -O-, -S- or $-S(O)_2-$, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O-, -S- or $-S(O)_2-$, wherein R is hydrogen or (C_{1-6})alkyl. For example, the instance wherein R^1 and R^2 together with the carbon atom to which both R^1 and R^2 are attached form hetero(C_{3-8})cycloalkyl" includes, but is not limited to, the following:



in which R is hydrogen, (C_{1-6})alkyl, or a protecting group.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C_{5-10})aryl as used in this Application includes, but is not limited to, 4-amino-2-hydroxypyrimidin-5-yl, benzothiazol-2-yl, 1*H*-benzoimidazol-2-yl, 2-bromopyrid-5-yl, 5-bromopyrid-2-yl, 4-carbamoylthiazol-2-yl, 3-carboxypyrid-4-yl, 5-carboxy-2,6-dimethylpyrid-3-yl, 3,5-dimethylisoxazol-4-yl, 5-ethoxy-2,6-dimethylpyrid-3-yl, 5-fluoro-6-hydroxypyrimidin-4-yl, fur-2-yl, fur-3-yl, 5-hydroxy-4,6-dimethylpyrid-3-yl, 8-hydroxy-5,7-dimethylquinolin-2-yl, 5-hydroxymethylisoxazol-3-yl, 3-hydroxy-6-methylpyrid-2-yl, 3-hydroxypyrid-2-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-indol-3-yl, isothiazol-4-yl, isoxazol-4-yl, 2-methylfur-3-yl, 5-methylfur-2-yl, 1-methyl-1*H*-imidazol-2-yl, 5-methyl-3*H*-imidazol-4-yl, 5-methylisoxazol-3-yl, 5-methyl-2*H*-pyrazol-3-yl, 3-methylpyrid-2-yl, 4-methylpyrid-2-yl, 5-methylpyrid-2-yl, 6-methylpyrid-2-yl, 2-methylpyrid-3-yl, 2-methylthiazol-4-yl, 5-nitropyrid-2-yl, 2*H*-pyrazol-3-yl, 3*H*-pyrazol-4-yl, pyridazin-3-yl,

pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-pyrid-3-yl-2*H*-[1,2,4]triazol-3-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1*H*-pyrrol-3-yl, quinolin-2-yl, 1*H*-tetrazol-5-yl, thiazol-2-yl, thiazol-5-yl, thien-2-yl, thien-3-yl, 2*H*-[1,2,4]triazol-3-yl, 3*H*-[1,2,3]triazol-4-yl, 5-trifluoromethylpyrid-2-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Optionally substituted hetero(C_{5-10})aryl as used in this Application to define R^4 includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, optionally substituted hetero(C_{8-10})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, and the like. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 3,4-dihydro-2*H*-quinolinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinylyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, 5,6,7,8-tetrahydroquinolinyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term hetero(C_{5-10})cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Both the unprotected and protected derivatives fall within the scope of the invention.

"Heteromonocyclic ring" means a saturated or partially unsaturated, monocyclic ring assembly containing the number of ring carbon atoms indicated, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by one or more heteroatoms selected from -N=, -NY^3-, -O- or -S-, wherein Y^3 is hydrogen, alkyl, aryl, arylalkyl, -C(=O)-R^{14}, -C(=O)-OR^{14} or -SO_2R^{14}.

"Heterobicyclic ring" means a saturated or partially unsaturated fused bicyclic or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by one or more heteroatoms selected from -N=, $-NY^3-$, -O- or -S-, wherein Y^3 is hydrogen, alkyl, aryl, arylalkyl, $-C(=O)-R^{14}$, $-C(=O)-OR^{14}$ or $-SO_2R^{14}$.

"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like.

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C_{1-6})alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where *n* is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name *N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide is meant to include (S)-*N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (R)-*N*-[1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide,

(R)-*N*-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (S)-*N*-[(R)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (R)-*N*-[(R)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, *N*-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, *N*-[(R)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (S)-*N*-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide and any mixture, racemic or otherwise, thereof.

"Ketone derivative" means a derivative containing the moiety -C(O)-. For example, in this Application X^3 can be 2-acetoxy-azetidin-3-yl. The "carbocyclic ketone derivative" of this example of X^3 would be 2-acetoxy-4-oxo-azetidin-3-yl (see Table 3, C32).

"Nitro" means the radical $-NO_2$.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein within R^3 and R^4 any alicyclic or aromatic ring system may be substituted further by 1-5 radicals…" means that R^3 and R^4 may or may not be substituted in order to fall within the scope of the invention.

"Oxoalkyl" means alkyl, as defined above, wherein one of the number of carbon atoms indicated is replaced by an oxygen group (-O-), e.g., oxo(C_{2-6})alkyl includes methoxymethyl, etc.

"*N*-oxide derivatives" means derivatives of compounds of Formula I in which nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids

such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound of Formula I containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of Formula I containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. Suitable esters of compounds of Formula I containing a carboxy group, are for example those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an

alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

"Treatment" or "treating" means any administration of a compound of the present invention and includes:

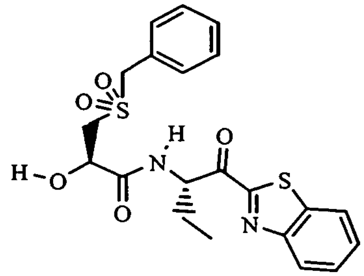
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Nomenclature:

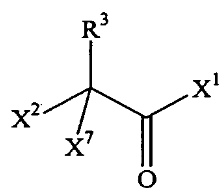
The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNom 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I wherein X^2 is hydroxy, R^3 is phenylmethanesulfonylmethyl and X^1 is $-NHC(R^1)(R^2)X^3$ (in which R^1 is hydrogen, R^2 is ethyl and X^3 is 1-benzothiazol-2-yl-methanoyl); that is, a compound having the following structure:



is named (R)-*N*-[(S)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide;

Presently Preferred Embodiments:

While the scope of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred. For example, preferred is a compound of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is hydrogen, fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH{=}CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^5 is hydrogen, (C_{1-4})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl; R^6 is hydrogen, hydroxy or (C_{1-6})alkyl; or where X^3 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl or hetero(C_{8-10})bicycloaryl; R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$; R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or (C_{5-10})heteroaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then X^2 is hydrogen,

fluoro, -OH, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

wherein within R^5, X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl,

(C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5, R^{12} and R^{13} are as defined above;

R^3 is (C_{1-6})alkyl or $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6})alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5, R^{12}, R^{13} and R^{14} are as defined above;

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $–X^8NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^8 is (C_{1-6})alkylene and X^5, R^{12}, R^{13} and R^{14} are as defined above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-3})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

R^{15} is (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl;

R^{17} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then R^{17} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

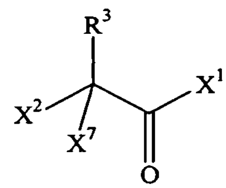
R^{18} is hydrogen, (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-6})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl, with the proviso that when X^3 is cyano, then R^{18} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl; and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8})heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or –O-, wherein the ring is unsubstituted or substituted with R^2, wherein R^2 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12}, R^{13} and R^{14} are as defined above;

wherein within R^3, R^4, R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any aromatic ring system present within R^{14} or R^{18} is not substituted further by halo, (C_{3-10})cycloalkyl, hetero(C_{3-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl; with the proviso that only one bicyclic ring structure is present within R^3, R^4 or R^{15}; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives,

individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Preferred is a compound of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is hydrogen, fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^3 is $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH{=}CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^5 is hydrogen, $(C_{1\text{-}4})$alkyl, $(C_{3\text{-}10})$cycloalkyl$(C_{0\text{-}6})$alkyl, hetero$(C_{3\text{-}10})$cycloalkyl$(C_{0\text{-}3})$alkyl, $(C_{6\text{-}10})$aryl$(C_{0\text{-}6})$alkyl, hetero$(C_{5\text{-}10})$aryl$(C_{0\text{-}6})$alkyl, $(C_{9\text{-}10})$bicycloaryl$(C_{0\text{-}6})$alkyl or hetero$(C_{8\text{-}10})$bicycloaryl$(C_{0\text{-}6})$alkyl; R^6 is hydrogen, hydroxy or $(C_{1\text{-}6})$alkyl; or where X^3 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both attached, form hetero$(C_{3\text{-}10})$cycloalkyl, hetero$(C_{5\text{-}10})$aryl or hetero$(C_{8\text{-}10})$bicycloaryl; R^7 is hydrogen or $(C_{1\text{-}4})$alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^{16} is hydrogen, $-X^4$, $-CF_3$, $-CF_2CF_2R^9$ or $-N(R^6)OR^6$; R^9 is hydrogen, halo, $(C_{1\text{-}4})$alkyl, $(C_{5\text{-}10})$aryl$(C_{0\text{-}6})$alkyl or $(C_{5\text{-}10})$heteroaryl$(C_{0\text{-}6})$alkyl;

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof, with the proviso that when $-X^4$ is other than a heteromonocyclic ring containing 5 ring member atoms, wherein no more than two of the ring member atoms comprising the ring are heteroatoms, then X^2 is fluoro, -OH, $-OR^4$, $-NHR^{15}$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

wherein within R^5, X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from $(C_{1\text{-}6})$alkyl, $(C_{1\text{-}6})$alkylidene,

cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5, R^{12} and R^{13} are as defined above;

R^3 is $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6})alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$,

$-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5, R^{12}, R^{13} and R^{14} are as defined above;

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $–X^8NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^8 is (C_{1-6})alkylene and X^5, R^{12}, R^{13} and R^{14} are as defined above;

R^{15} is (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl;

R^{17} is hydrogen, (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

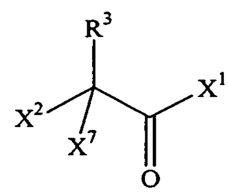
R^{18} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-6})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl; and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8})heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or -O-, wherein the ring is unsubstituted or substituted with R^1, wherein R^1 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12}, R^{13} and R^{14} are as defined above;

wherein within R^3, R^4, R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$,

$-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above; with the proviso that only one bicyclic ring structure is present within R^3, R^4 or R^{15}; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Preferred is a compound of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is hydrogen, fluoro, -OH, $-OR^4$ or $-NR^{17}R^{18}$ and X^7 is hydrogen or X^2 and X^7 both represent fluoro;

X^3 is cyano;

wherein within X^3 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$,

$-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5R^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5, R^{12} and R^{13} are as defined above;

R^3 is $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6})alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5, R^{12}, R^{13} and R^{14} are as defined above;

R^4 is selected from $-X^8NR^{12}R^{12}$, $-X^8NR^{12}C(O)R^{12}$, $-X^8NR^{12}C(O)OR^{12}$, $-X^8NR^{12}C(O)NR^{12}R^{12}$, $-X^8NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^8OR^{12}$, $-X^8SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^8OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^8S(O)_2NR^{12}R^{12}$, $-X^8NR^{12}S(O)_2R^{12}$, $-X^8P(O)(OR^{12})OR^{12}$, $-X^8OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^8NR^{12}C(O)R^{13}$, $-X^8S(O)R^{13}$, $-X^8S(O)_2R^{13}$, $-R^{14}$, $-X^8OR^{14}$, $-X^8SR^{14}$, $-X^8S(O)R^{14}$, $-X^8S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^8OC(O)R^{14}$, $-X^8NR^{14}R^{12}$, $-X^8NR^{12}C(O)R^{14}$, $-X^8NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^8S(O)_2NR^{14}R^{12}$, $-X^8NR^{12}S(O)_2R^{14}$, $-X^8NR^{12}C(O)NR^{14}R^{12}$ and $-X^8NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^8 is (C_{1-6})alkylene and X^5, R^{12}, R^{13} and R^{14} are as defined above, with the proviso that when X^3 is cyano and X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, then R^{14} is (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-3})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

R^{15} is (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl;

R^{17} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl;

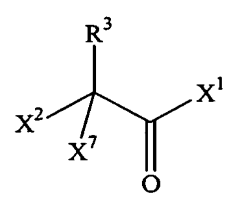
R^{18} is (C_{1-6})alkyl, (C_{3-10})cycloalkyl(C_{1-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{1-6})alkyl, (C_{6-10})aryl(C_{1-6})alkyl, hetero(C_{5-10})aryl(C_{1-6})alkyl, (C_{9-10})bicycloaryl(C_{1-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{1-6})alkyl; and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8})heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or $-O-$, wherein the ring is unsubstituted or substituted with R^1, wherein R^1 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12}, R^{13} and R^{14} are as defined above;

wherein within R^3, R^4, R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$,

$-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above, with the proviso that when X^2 is $-OR^4$, where R^4 is defined as $-R^{14}$, or $-NHR^{18}$, then any aromatic ring system present within R^{14} or R^{18} is not substituted further by halo, (C_{3-10})cycloalkyl, hetero(C_{3-10})cycloalkyl, (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl; with the proviso that only one bicyclic ring structure is present within R^3, R^4 or R^{15}; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Preferred is a compound of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$;

X^2 is -OH, $-OC(O)NR^{12}R^{12}$ or $-OC(O)R^{14}$, wherein R^{12} and R^{14} are as defined below;

X^3 is cyano, $-C(R^7)(R^8)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH_2C(O)R^{16}$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^5 is hydrogen, (C_{1-4})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl; R^6 is hydrogen, hydroxy or (C_{1-6})alkyl; or where X^3 contains an $-NR^5R^6$ group, R^5 and R^6 together with the nitrogen atom to which they are both

attached, form hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl or hetero(C_{8-10})bicycloaryl; R^7 is hydrogen or (C_{1-4})alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^{16} is hydrogen, -X^4, -CF_3, -$CF_2CF_2R^9$ or -$N(R^6)OR^6$; R^9 is hydrogen, halo, (C_{1-4})alkyl, (C_{5-10})aryl(C_{0-6})alkyl or (C_{5-10})heteroaryl(C_{0-6})alkyl;

X^4 comprises a heteromonocyclic ring containing 4 to 7 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof;

wherein within R^5, X^3 or X^4 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, -$X^5NR^{12}R^{12}$, -$X^5NR^{12}C(O)R^{12}$, -$X^5NR^{12}C(O)OR^{12}$, -$X^5NR^{12}C(O)NR^{12}R^{12}$, -$X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, -$X^5OR^{12}$, -$X^5SR^{12}$, -$X^5C(O)OR^{12}$, -$X^5C(O)R^{12}$, -$X^5OC(O)R^{12}$, -$X^5C(O)NR^{12}R^{12}$, -$X^5S(O)_2NR^{12}R^{12}$, -$X^5NR^{12}S(O)_2R^{12}$, -$X^5P(O)(OR^{12})OR^{12}$, -$X^5OP(O)(OR^{12})OR^{12}$, -$X^5NR^{12}C(O)R^{13}$, -$X^5S(O)R^{13}$ and -$X^5S(O)_2R^{13}$ and/or 1 radical selected from -R^{14}, -X^5OR^{14}, -X^5SR^{14}, -$X^5S(O)R^{14}$, -$X^5S(O)_2R^{14}$, -$X^5C(O)R^{14}$, -$X^5C(O)OR^{14}$, -$X^5OC(O)R^{14}$, -$X^5NR^{14}R^{12}$, -$X^5NR^{12}C(O)R^{14}$, -$X^5NR^{12}C(O)OR^{14}$, -$X^5C(O)NR^{12}R^{12}$, -$X^5S(O)_2NR^{14}R^{12}$, -$X^5NR^{12}S(O)_2R^{14}$, -$X^5NR^{12}C(O)NR^{14}R^{12}$ and -$X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from a group consisting of hydrogen, cyano, -$X^5NR^{12}R^{12}$, -$X^5NR^{12}C(O)R^{12}$, -$X^5NR^{12}C(O)OR^{12}$, -X^5R^{12}, -$X^5NR^{12}C(O)NR^{12}R^{12}$, -$X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, -$X^5OR^{12}$, -$X^5SR^{12}$, -$X^5C(O)OR^{12}$, -$X^5C(O)R^{12}$, -$X^5OC(O)R^{12}$, -$X^5C(O)NR^{12}R^{12}$, -$X^5S(O)_2NR^{12}R^{12}$, -$X^5NR^{12}S(O)_2R^{12}$, -$X^5P(O)(OR^{12})OR^{12}$, -$X^5OP(O)(OR^{12})OR^{12}$, -$X^5NR^{12}C(O)R^{13}$, -$X^5S(O)R^{13}$, -$X^5S(O)_2R^{13}$, -$R^{14}$, -$X^5OR^{14}$, -$X^5SR^{14}$, -$X^5S(O)R^{14}$, -$X^5S(O)_2R^{14}$, -$X^5C(O)R^{14}$, -$X^5C(O)OR^{14}$, -$X^5OC(O)R^{14}$, -$X^5NR^{14}R^{12}$, -$X^5NR^{12}C(O)R^{14}$, -$X^5NR^{12}C(O)OR^{14}$, -$X^5C(O)NR^{12}R^{12}$, -$X^5S(O)_2NR^{14}R^{12}$, -$X^5NR^{12}S(O)_2R^{14}$, -$X^5NR^{12}C(O)NR^{14}R^{12}$ and -$X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl,

(C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$ and $-X^5C(O)R^{13}$, wherein X^5, R^{12} and R^{13} are as defined above;

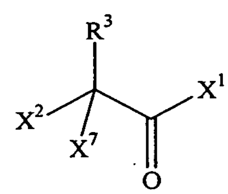
R^3 is $-C(R^6)(R^6)X^6$, wherein R^6 is hydrogen or (C_{1-6})alkyl and X^6 is selected from $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5C(O)R^{13}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5S(O)_2R^{13}$, $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$ wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; and

R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form (C_{4-8})heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or –O-, wherein and the ring is unsubstituted or substituted with R^1, wherein R^1 is as defined above, and R^{21} is hydrogen, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$, $-S(O)R^{14}$, $-S(O)_2R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)NR^{12}R^{12}$ and $-S(O)_2NR^{14}R^{12}$, wherein R^{12}, R^{13} and R^{14} are as defined above;

wherein within R^3, R^4, R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{14}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$,

$-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above; with the proviso that only one bicyclic ring structure is present within R^3, R^4 or R^{15}; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Preferred is a compound of Formula I:



I

in which:

X^1 is $-NHC(R^1)(R^2)\ C(O)C(O)NR^5R^6$, wherein R^5 is hydrogen, (C_{1-4})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl and R^6 is hydrogen, hydroxy or (C_{1-6})alkyl or R^5 and R^6 together with the nitrogen atom to which they are both attached form hetero(C_{3-10})cycloalkyl, hetero(C_{5-10})aryl or hetero(C_{8-10})bicycloaryl;

X^2 is hydrogen;

wherein within X^1 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$, $-X^5SR^{14}$, $-X^5S(O)R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)OR^{14}$, $-X^5OC(O)R^{14}$, $-X^5NR^{14}R^{12}$, $-X^5NR^{12}C(O)R^{14}$, $-X^5NR^{12}C(O)OR^{14}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{14}R^{12}$, $-X^5NR^{12}S(O)_2R^{14}$, $-X^5NR^{12}C(O)NR^{14}R^{12}$ and $-X^5NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^5 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence

independently is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; R^{13} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl; and R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-10})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-10})bicycloaryl(C_{0-6})alkyl;

R^1 is hydrogen and R^2 is (C_{1-6})alkyl; and

R^3 is $-CH_2X^6$, wherein X^6 is $-X^5NR^{12}S(O)_2R^{12}$ or $-X^5S(O)_2R^{14}$ wherein X^5, R^{12} and R^{14} are as defined above;

wherein within R^3 any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^5NR^{12}R^{12}$, $-X^5NR^{12}C(O)R^{12}$, $-X^5NR^{12}C(O)OR^{12}$, $-X^5NR^{12}C(O)NR^{12}R^{12}$, $-X^5NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^5OR^{12}$, $-X^5SR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{12}$, $-X^5OC(O)R^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$, $-X^5P(O)(OR^{12})OR^{12}$, $-X^5OP(O)(OR^{12})OR^{12}$, $-X^5NR^{12}C(O)R^{13}$, $-X^5S(O)R^{13}$, $-X^5C(O)R^{13}$ and $-X^5S(O)_2R^{13}$ and within R^3 any aliphatic moiety is unsubstituted or substituted further by 1 to 5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{12}$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$, $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^5, R^{12}, R^{13} and R^{14} are as described above; with the proviso that only one bicyclic ring structure is present within R^3; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Preferred are compounds of the invention in which X^1 is $-NHC(R^1)(R^2)X^3$ or $-NHCH(R^{19})C(O)R^{20}$, wherein R^1 is hydrogen or (C_{1-6})alkyl and R^2 is hydrogen, (C_{1-6})alkyl, $-X^5OR^{12}$, $-X^5S(O)R^{13}$, $-X^5OR^{14}$, (C_{6-10})aryl(C_{0-6})alkyl or hetero(C_{5-10})aryl(C_{0-6})alkyl or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-6})cycloalkylene or (C_{3-6})heterocycloalkylene, wherein within said R^2 any heteroaryl, aryl, cycloalkylene or heterocycloalkylene is unsubstituted or substituted with (C_{1-6})alkyl or hydroxy, particularly wherein X^3 is cyano, $-C(O)R^{16}$, $-C(R^6)(OR^6)_2$, $-CH{=}CHS(O)_2R^5$, $-CH_2C(O)R^{16}$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$, wherein R^5, R^6 and R^{16} are as described above, and R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form

(C_{4-8})heterocycloalkylene, wherein no more than one of the ring member atoms comprising the ring is a heteroatom selected from $-NR^{21}-$ or -O-, particularly wherein the ring is unsubstituted or substituted with (C_{1-6})alkyl or $-X^5C(O)OR^{12}$ and R^{21} is hydrogen, (C_{1-6})alkyl, $-X^5C(O)R^{12}$, $-X^5C(O)OR^{12}$, $-R^{14}$, $-X^5C(O)R^{14}$ or $-C(O)OR^{14}$.

Particularly preferred are compounds of the invention in which X^3 is cyano, $-C(O)X^4$, -C(O)H, $-C(O)N(CH_3)OCH_3$, $-CH(OCH_3)_2$, $-C(O)CF_3$, $-C(O)CF_2CF_3$, $-CH_2C(O)R^{16}$, (E)-2-benzenesulfonyl-vinyl, 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1□^{6}-thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl, 1-benzoyl-piperidin-4-ylaminooxalyl, 1-benzylcarbamoyl-methanoyl, 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl, 2-oxo-2-phenyl-ethanoyl, 3*H*-oxazole-2-carbonyl, 5-trifluoromethyl-oxazole-2-carbonyl, 3-trifluoromethyl-[1,2,4]oxadiazole-5-carbonyl, 2,2,3,3,3-pentafluoro-propionyl, hydroxyaminooxalyl, oxalyl, 2-(1,3-dihydro-isoindol-2-yl)-2-oxo-acetyl, benzothiazol-2-ylaminooxalyl, 2-oxo-ethyl, 2-oxazol-2-yl-2-oxo-ethyl or 2-benzooxazol-2-yl-2-oxo-ethyl, particularly wherein X^4 is 1*H*-benzoimidazol-2-yl, pyrimidin-2-yl, benzooxazol-2-yl, benzothiazol-2-yl, pyridazin-3-yl, 3-phenyl-[1,2,4]oxadiazol-5-yl or 3-ethyl-[1,2,4]oxadiazol-5-yl; and R^{19} and R^{20} together with the atoms to which R^{19} and R^{20} are attached form 1-benzoyl-3-oxo-piperidin-4-yl, 1-benzoyl-3-oxo-azepan-4-yl, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-1-(1-phenyl-methanoyl)-pyrrolidin-3-yl or (S)-2-acetoxy-4-oxo-azetidin-3-yl.

Most particularly preferred are compounds of the invention in which X^3 is $-C(O)X^4$, in particular 1*H*-benzoimidazol-2-ylcarbonyl, pyrimidin-2-ylcarbonyl, benzooxazol-2-ylcarbonyl, benzothiazol-2-ylcarbonyl, pyridazin-3-ylcarbonyl, 3-phenyl-[1,2,4]oxadiazol-5-ylcarbonyl or 3-ethyl-[1,2,4]oxadiazol-5-ylcarbonyl, or $-C(O)C(O)NR5R^6$, in particular 2-oxo-2-pyrrolidin-1-yl-acetyl, 2-morpholin-4-yl-2-oxo-acetyl, 2-oxo-2-piperazin-1-yl-acetyl, 2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-acetyl, 2-(1,1-dioxo-1□^{6}-thiomorpholin-4-yl)-2-oxo-acetyl, dimethylaminooxalyl, tetrahydro-pyran-4-ylaminooxalyl, 2-morpholin-4-yl-ethylaminooxalyl, cyclopentyl-ethyl-aminooxalyl, pyridin-3-ylaminooxalyl, phenylaminooxalyl or 1-benzoyl-piperidin-4-ylaminooxalyl.

Preferred are compounds of the invention in which X^2 is -OH or $-OC(O)NR^{12}R^{12}$,

particularly wherein each R^{12} independently represent hydrogen or (C_{1-6})alkyl, wherein said alkyl is unsubstituted or substituted with hydroxy or methoxy, or X^2 is -OC(O)NHR^{14}, wherein R^{14} is (C_{3-10})cycloalkyl(C_{0-6})alkyl or hetero(C_{3-10})cycloalkyl(C_{1-3})alkyl, or X^2 is -OC(O)R^{14}, wherein R^{14} is -NR^{22}R^{23} and R^{22} and R^{23} together with the nitrogen atom to which both R^{22} and R^{23} attached form a hetero(C_{4-6})cycloalkyl ring, which ring may be unsubstituted or substituted with hydroxy, particularly in which X^2 is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino, 4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-benzyl-carbamoyloxy, pyrrolidin-1-yl-carbonyloxy, *N,N*-dimethyl-carbamoyloxy, piperidin-1-yl-carbonyloxy, 4-methanesulfonyl-piperazin-1-yl-carbonyloxy, 4-ethoxycarbonylpiperazin-1-ylcarbonyloxy, *N*-cyclohexyl-carbamoyloxy, *N*-phenyl-carbamoyloxy, *N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-carbamoyloxy, *N*-butyl-*N*-methyl-carbamoyloxy, *N*-pyridin-3-yl-carbamoyloxy, *N*-isopropyl-carbamoyloxy, *N*-pyridin-4-yl-carbamoyloxy, *N*-cyanomethyl-*N*-methyl-carbamoyloxy, *N,N*-bis-(2-methoxy-ethyl)-carbamoyloxy, *N*-phenethyl-carbamoyloxy, piperazine- carbonyloxy, *N*-naphthalen-2-yl-carbamoyloxy, 4-benzyl-piperazine-1-carbamoyloxy, 4-(1-furan-2-yl-carbonyl)-piperazine-1-carbamoyloxy, thiomorpholin-4-yl- carbonyloxy, 1,1-dioxo-1λ^6-thiomorpholin-4-yl)- carbonyloxy, bis-(2-methoxy-ethyl)-carbamoyloxy, morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy and carbamoyloxy, more particularly morpholin-4-ylcarbonyloxy, 2-methoxyethylcarbamoyloxy, diethylcarbamoyloxy, pyrrolidin-1-ylcarbonyloxy, 2-hydroxyethylcarbamoyloxy, tetrahydro-furan-2-ylmethylcarbamoyloxy, cyclopropylcarbamoyloxy, *tert*-butylcarbamoyloxy, 3-hydroxy-pyrrolidin-1-yl-carbonyloxy and carbamoyloxy.

Preferred are compounds of the invention in which X^2 is -NHR^{15}, wherein R^{15} is (C_{6-10})aryl, hetero(C_{5-10})aryl, (C_{9-10})bicycloaryl or hetero(C_{8-10})bicycloaryl, or -NR^{17}R^{18}, wherein R^{17} is hetero(C_{3-10})cycloalkyl and R^{18} is hydrogen or R^{17} and R^{18} independently are (C_{6-10})aryl(C_{1-6})alkyl or hetero(C_{5-10})aryl(C_{1-6})alkyl, wherein within R^{15}, R^{17} and R^{18} any alicyclic or aromatic ring system is unsubstituted or substituted further by 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted(C_{1-4})alkyl,

$-X^5OR^{12}$, $-X^5C(O)OR^{12}$, $-X^5C(O)R^{13}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5NR^{12}S(O)_2R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^5OR^{14}$ and $-X^5C(O)NR^{14}R^{12}$, in particular in which X^2 is selected from 5-nitrothiazol-2-ylamino, 2-nitrophenylamino, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, 1-methyl-piperidin-4-ylamino, isopropylamino, di(thien-2-ylmethyl)amino or di(benzyl)amino.

Preferred are compounds of the invention in which X^2 is $-OR^4$ wherein R^4 is 4-methoxy-phenyl, 4'-hydroxymethyl-phenyl, methoxymethyl, phenyl-methanoyl, 1-(4-phenoxy-phenyl)-methanoyl, 3-biphenyl, 4-biphenyl, 1-biphenyl-4-yl-methanoyl, naphthalen-2-yl-methanoyl, benzo[1,3]dioxol-5-yl-methanoyl, (4-methanesulfonylamino-phenyl)-methanoyl, benzo[*b*]thien-2-yl-methanoyl, 4'-chloro-4-biphenyl, 4-hydroxy-phenyl-methanoyl, 3-chloro-benzo[*b*]thien-2-yl-methanoyl, thien-2-yl-methanoyl, thien-3-yl-methanoyl, 3-chloro-thien-2-yl-methanoyl, 5-methyl-thien-2-yl-methanoyl, 4-methoxy-phenyl methanoyl, 4-trifluoromethoxy-phenyl methanoyl, 4-chloro-phenyl-methanoyl, 3-bromo-phenyl, cyclohexylmethyl, 3,4-dimethoxy-phenyl-methanoyl, 3,4-difluorophenyl-methanoyl, 3-fluoro, 4-methoxy-phenyl-methanoyl, 4-fluorophenyl-methanoyl, 4-trifluoromethyl-phenyl-methanoyl, 4-formyl-phenyl-formyl, 3-formyl-phenyl-formyl, 4-methyl-pentanoyl, tetrahydro-pyran-4-ylmethyl 2-morpholin-4-yl-2-oxo-ethyl.

Most particularly preferred are compounds of the invention in which X^2 is selected from -OH, dimethylcarbamoyloxy, morpholin-4-ylcarbonyloxy, piperidin-1-yl-carbonyloxy, pyrrolidin-1-yl-carbonyloxy, pyrimidin-2-ylamino, tetrahydro-pyran-4-ylamino, 1-methyl-piperidin-4-ylamino, *N*-(2-methoxyethyl)-*N*-(tetrahydro-pyran-4-yl)amino, isopropylamino and cyclohexylamino.

Preferred are compounds of the invention in which R^1 is hydrogen or (C_{1-6})alkyl and R^2 is hydrogen, $-X^5OR^{12}$, $-X^5R^{12}$, (C_{5-10})heteroaryl(C_{0-6})alkyl, (C_{5-10})aryl(C_{0-6})alkyl, (C_{5-10})cycloalkyl(C_{0-6})alkyl, (C_{5-10})heterocycloalkyl(C_{0-6})alkyl or (C_{1-6})alkyl; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6})alkyl and hydroxy; particularly in which R^1 is hydrogen or methyl and R^2 is hydrogen, methoxymethyl, (C_{1-6})alkyl, phenethyl, thien-2-yl or 5-methyl-furan-2-yl or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form cyclopropylene, tetrahydro-pyran-4-ylene or methyl-piperidin-4-ylene.

Preferred are compounds of the invention in which R^3 is $-CH_2X^6$; wherein X^6 is is selected from $-X^5SR^{12}$, $-X^5C(O)NR^{12}R^{12}$, $-X^5S(O)_2R^{13}$, $-X^5C(O)R^{13}$, $-X^5OR^{12}$, $-X^5SR^{14}$, $-X^5R^{14}$, $-X^5S(O)_2R^{14}$, $-X^5C(O)R^{14}$, $-X^5C(O)NR^{14}R^{12}$, wherein X^5, R^{12}, R^{13} and R^{14} are as defined above; particularly wherein R^3 is thiophene-2-sulfonyl-methyl, 3-chloro-2-fluoro-phenyl-methane-sulfonyl-methyl, benzene-sulfonyl-methyl, phenyl-methane-sulfonyl-methyl, 2-(1,1-difluoro-methoxy)-phenyl-methane-sulfonyl-methyl, 2-benzene-sulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-phenyl-methanesulfonyl-ethyl, oxy-pyridin-2-yl-methane-sulfonyl-methyl, prop-2-ene-1-sulfonyl-methyl, 4-methoxy-phenyl-methane-sulfonyl-methyl, *p*-tolyl-methane-sulfonyl-methyl, 4-chloro-phenyl-methane-sulfonyl-methyl, *o*-tolyl-methane-sulfonyl-methyl, 3,5-dimethyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 2-bromo-phenyl-methane-sulfonyl-methyl, pyridin-2-yl-methane-sulfonyl-methyl, pyridin-3-yl-methane-sulfonyl-methyl, pyridin-4-yl-methane-sulfonyl-methyl, naphthalen-2-yl-methane-sulfonyl-methyl, 3-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 3-trifluoro-methoxy-phenyl-methane-sulfonyl-methyl, 4-fluoro-2-trifluoromethoxy-phenyl-methane-sulfonylmethyl, 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl, 3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl, 2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl, 4-*tert*-butyl-phenylmethanesulfonylmethyl, 2-fluoro-3-methyl-phenyl-methane-sulfonyl-methyl, 3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethane-sulfonylmethyl, 2-chloro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethane-sulfonylmethyl, 2,6-difluoro-phenylmethanesulfonylmethyl, 2,5-dichloro-phenyl-methane-sulfonylmethyl, 3,4-dichloro-phenylmethanesulfonylmethyl, 2-(1,1-difluoro-methoxy)-phenyl-methanesulfonylmethyl, 2-cyano-phenyl-methane-sulfonyl-methyl, 3-cyano-phenylmethanesulfonylmethyl, 2-trifluoro-methoxy-phenyl-methane-sulfonylmethyl, 2,3-difluoro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenyl-methanesulfonylmethyl, biphenyl-2-ylmethanesulfonylmethyl, cyclohexylmethyl, 3-fluoro-phenyl-methanesulfonylmethyl, 3,4-difluoro-phenyl-methanesulfonylmethyl, 2,4-difluoro-phenylmethanesulfonylmethyl, 2,4,6-trifluoro-phenylmethanesulfonylmethyl, 2,4,5-trifluoro-phenylmethanesulfonylmethyl, 2,3,4-trifluoro-phenylmethanesulfonylmethyl, 2,3,5-trifluoro-phenyl-methane-sulfonylmethyl, 2,5,6-trifluoro-phenylmethanesulfonylmethyl,

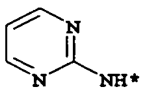
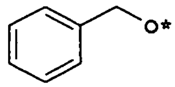
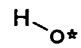
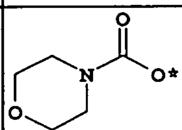
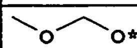
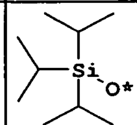
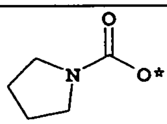
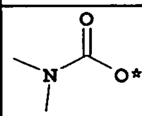
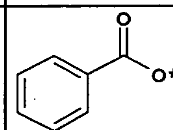
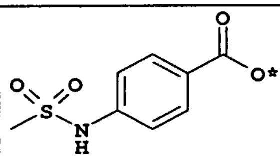
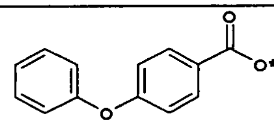
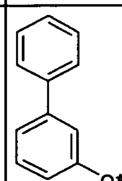
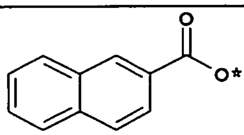
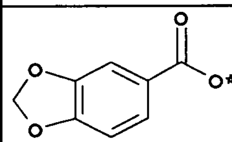
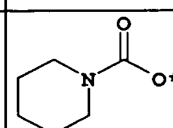
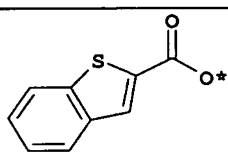
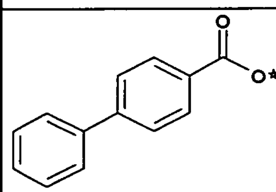
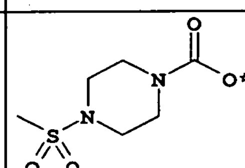
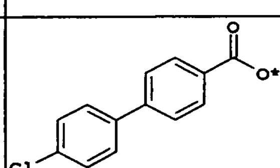
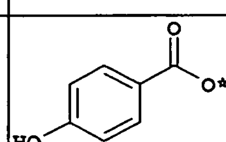
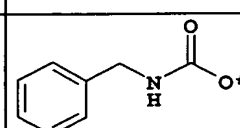
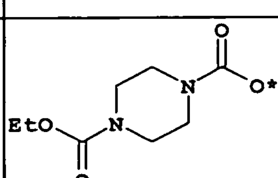
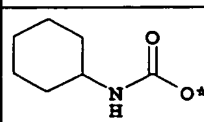
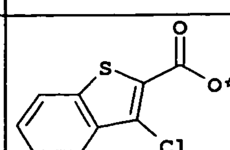
2-chloro-5-trifluoro-methylphenylmethanesulfonylmethyl, 2-methyl-propane-1-sulfonyl, 2-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl, 2-fluoro-4-trifluoro-methylphenylmethanesulfonylmethyl, 2-fluoro-5-trifluoro-methyl-phenyl-methane-sulfonyl-methyl, 4-fluoro-3-trifluoro-methylphenylmethanesulfonylmethyl, 2-methoxy-phenyl-methanesulfonylmethyl, 3,5-bis-trifluoromethyl-phenylmethanesulfonylmethyl, 4-difluoromethoxy-phenylmethanesulfonylmethyl, 2-difluoro-methoxy-phenyl-methanesulfonylmethyl, 3-difluoromethoxy-phenylmethanesulfonylmethyl, 2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl, 3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl, 5-chloro-thien-2-yl-methane-sulfonylmethyl, 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[2-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-[3-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl, 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-(2-trifluoro-methoxy-benzene-sulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl, biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl, 2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl, 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl, 2-trifluoromethyl-benzylsulfanylmethyl, phenylsulfanyl-ethyl, cyclopropyl-methanesulfonylmethyl, 5-bromo-thien-2-ylmethyl, 3-phenyl-propyl, 2,2-difluoro-3-phenyl-propyl, 3,4,5-trimethoxy-phenylmethanesulfonylmethyl, 2,2-difluoro-3-thien-2-yl-propyl, cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^5S(O)_2R^{13}$ and $-X^5S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted.

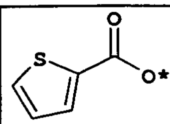
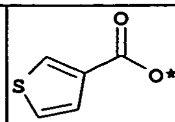
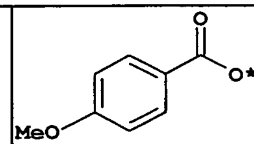
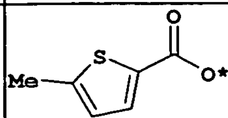
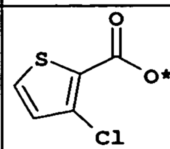
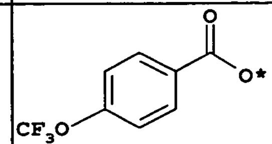
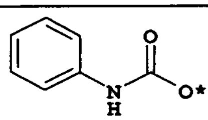
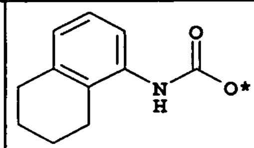
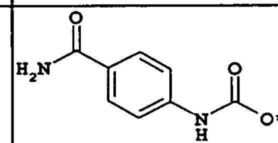
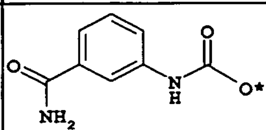
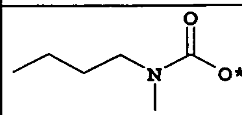
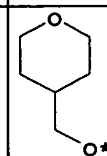
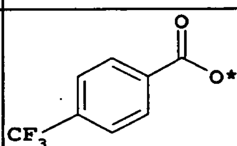
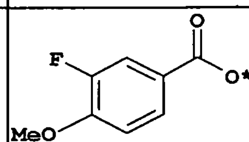
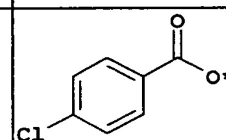
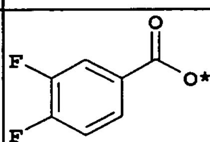
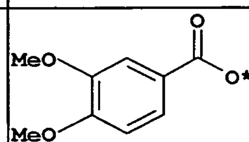
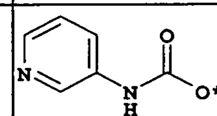
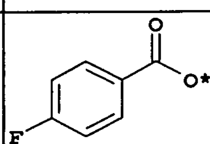
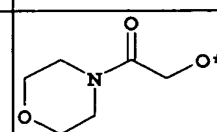
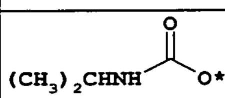
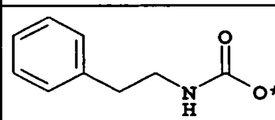
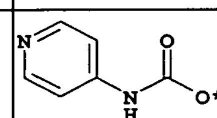
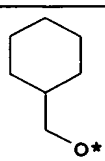
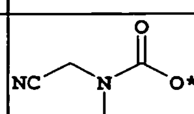
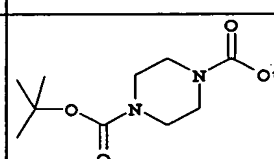
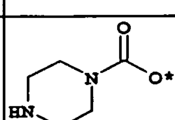
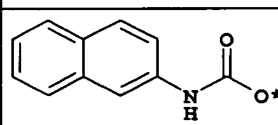
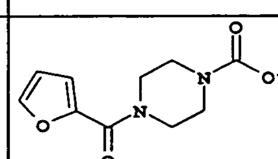
Preferred are compounds of the invention in which R^3 is cyclohexylethyl, cyclohexylmethyl, *tert*-butylmethyl, 1-methylcyclohexylmethyl, 1-methylcyclopentylmethyl, 2,2-difluoro-3-phenylpropyl, 2,2-dimethyl-3-phenylpropyl, 1-benzylcyclopropylmethyl, $-X^5S(O)_2R^{13}$ or $-X^5S(O)_2R^{14}$, wherein R^{13} is alkyl and R^{14} is phenyl which phenyl is unsubstituted or substituted.

The following tables are intended to provide guidance to better carry out the present invention. However, they do not limit the scope of the invention. People of ordinary skill may selectively make particular compounds by joining O*, HN* or H* of one of the fragments (A1 to A62) shown in Table 1 to the methine carbon atom (*CH*) of one of the fragments (B1 to

B93) shown in Table 2, and joining the methine carbon atom (*CH* or *CF*) of one of the fragments (B1 to B93) hown in Table 2 to the acyl carbon atom (C*) of one of the fragments (C1 to C91) depicted in Table 3.

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	
A22		A23		A24	

A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37		A38		A39	
A40		A41		A42	
A43		A44		A45	
A46		A47		A48	
A49		A50		A51	
A52		A53		A54	

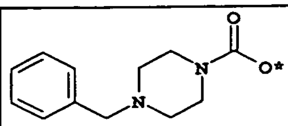
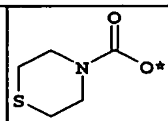
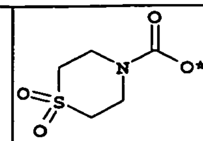
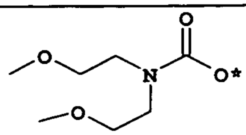
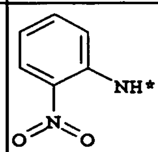
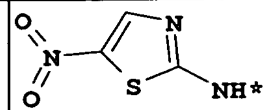
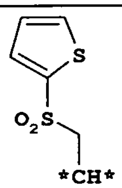
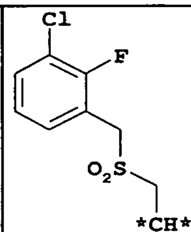
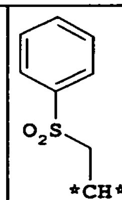
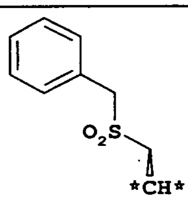
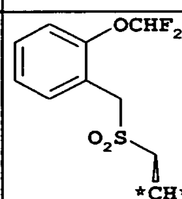
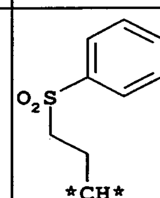
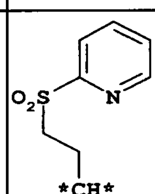
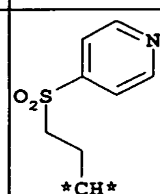
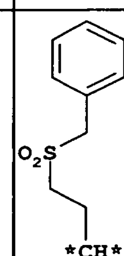
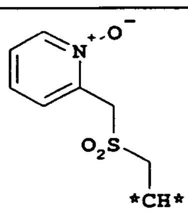
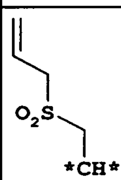
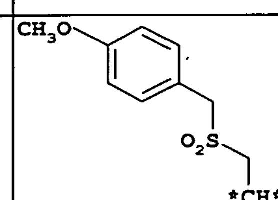
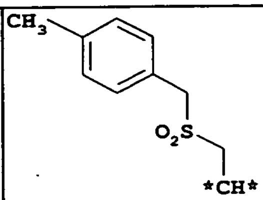
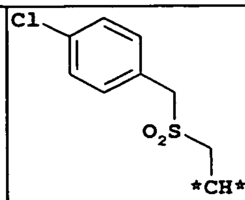
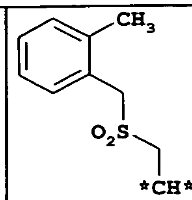
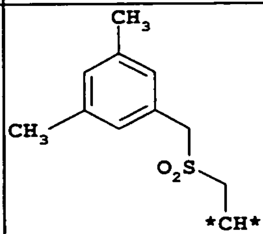
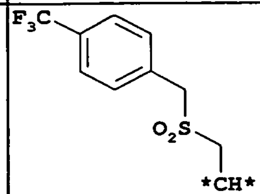
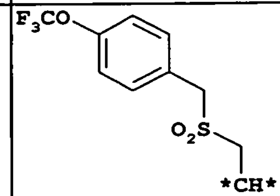
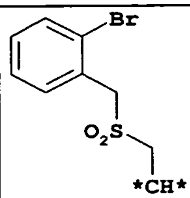
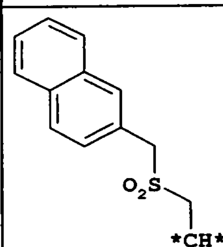
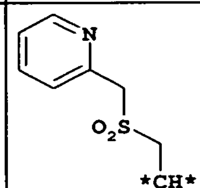
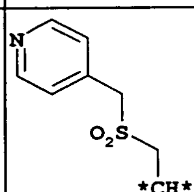
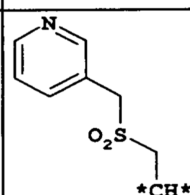
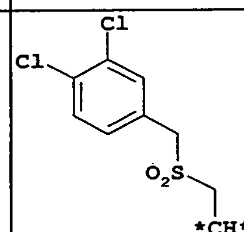
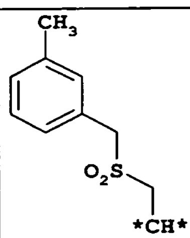
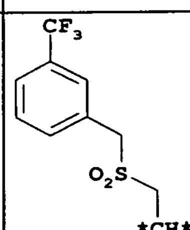
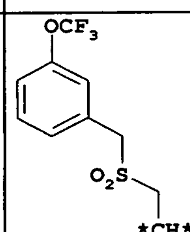
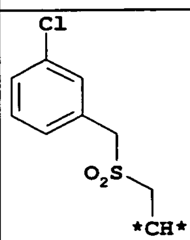
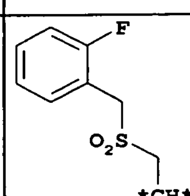
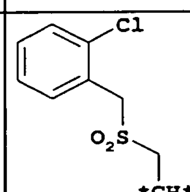
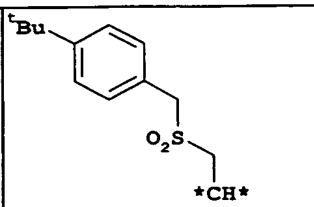
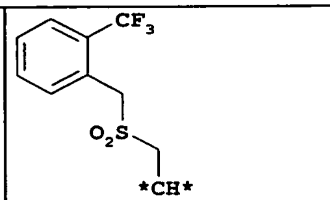
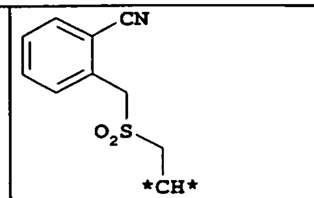
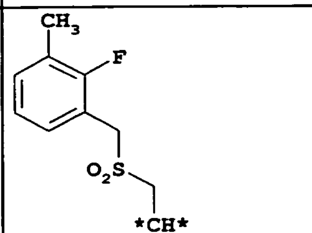
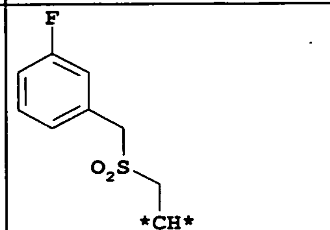
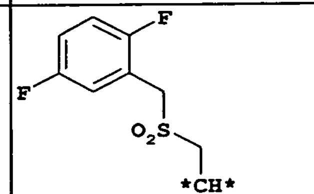
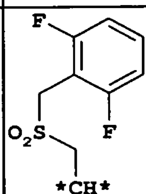
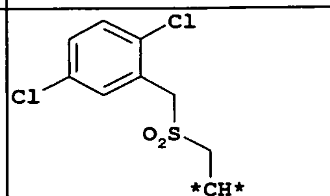
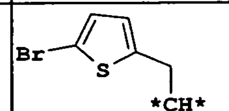
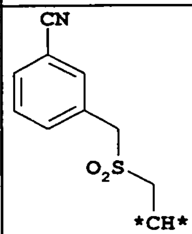
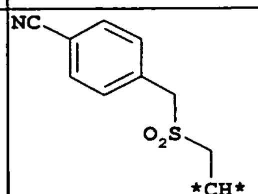
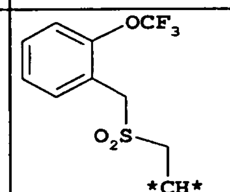
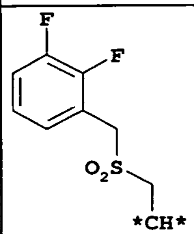
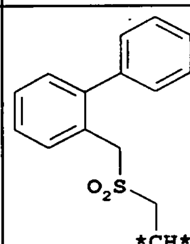
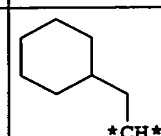
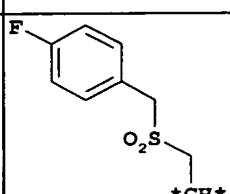
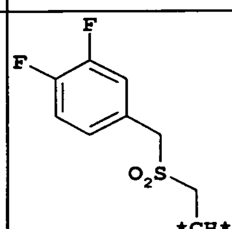
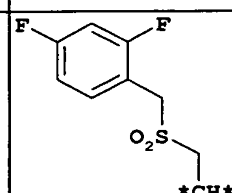
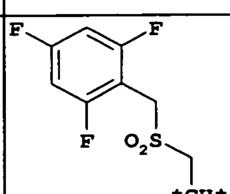
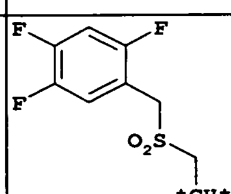
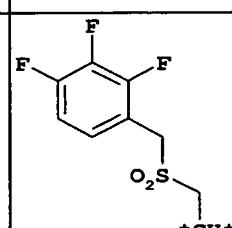
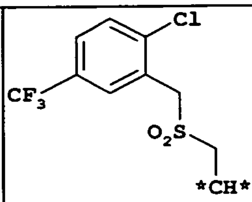
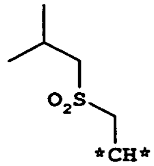
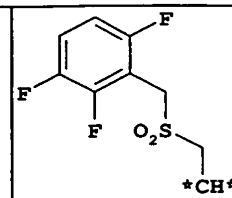
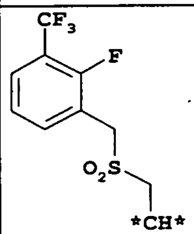
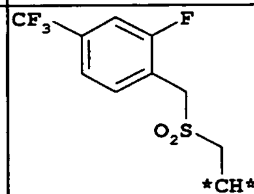
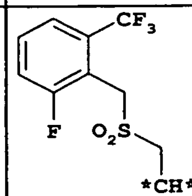
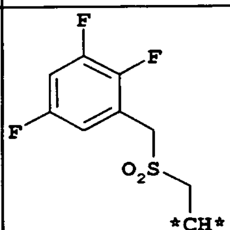
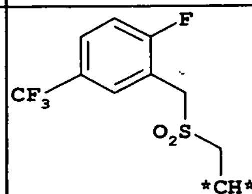
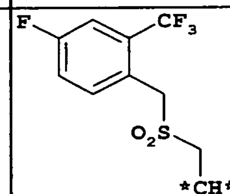
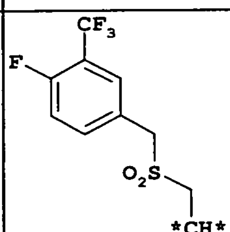
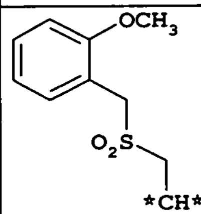
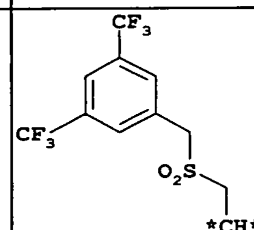
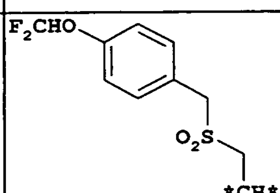
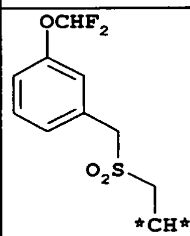
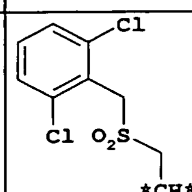
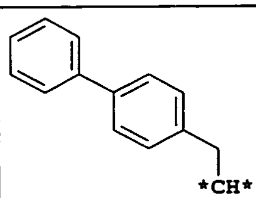
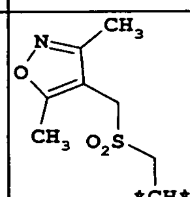
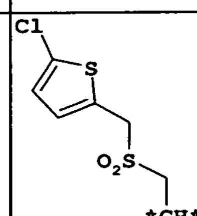
A55		A56		A57	
A58		A59		A60	
A61	H*	A62	F*		

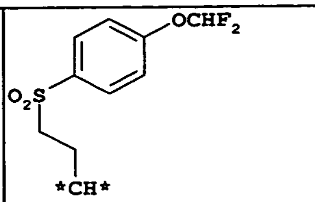
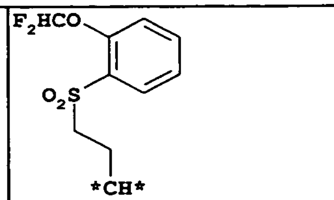
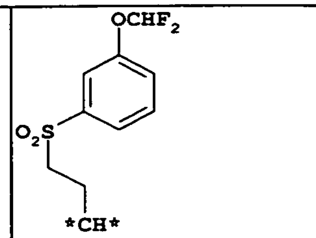
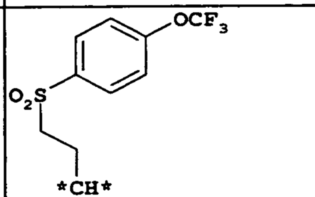
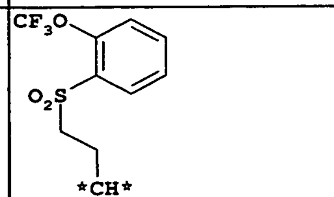
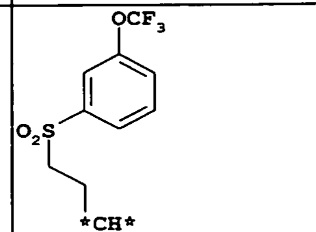
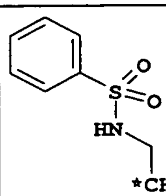
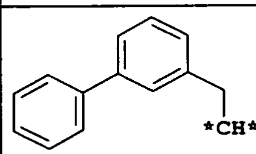
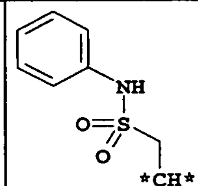
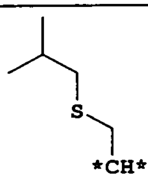
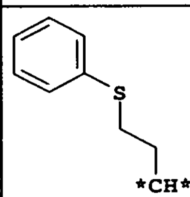
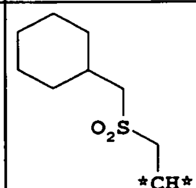
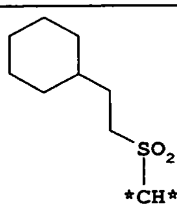
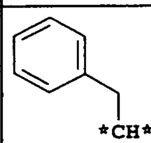
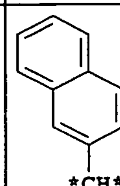
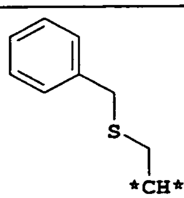
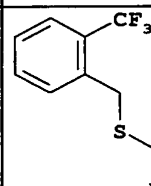
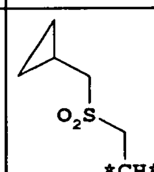
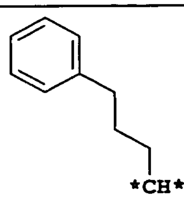
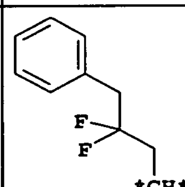
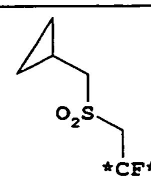
TABLE 2

B1		B2		B3	
B4		B5		B6	
B7		B8		B9	
B10		B11		B12	

B13		**B14**		**B15**	
B16		**B17**		**B18**	
B19		**B20**		**B21**	
B22		**B23**		**B24**	
B25		**B26**		**B27**	
B28		**B29**		**B30**	

B31		**B32**		**B33**	
B34		**B35**		**B36**	
B37		**B38**		**B39**	
B40		**B41**		**B42**	
B43		**B44**		**B45**	
B46		**B47**		**B48**	
B49		**B50**		**B51**	

B52		B53		B54	
B55		B56		B57	
B58		B59		B60	
B61		B62		B63	
B64		B65		B66	
B67		B68		B69	

B70		**B71**		**B72**	
B73		**B74**		**B75**	
B76		**B77**		**B78**	
B79		**B80**		**B81**	
B82		**B83**		**B84**	
B85		**B86**		**B87**	
B88		**B89**		**B90**	

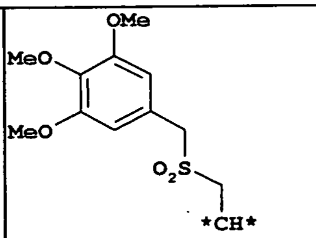
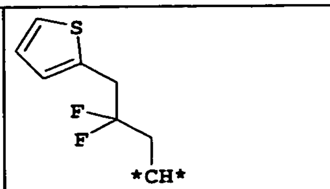
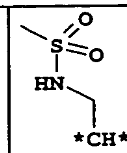
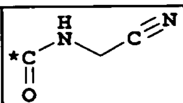
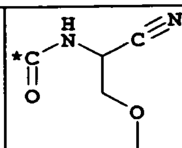
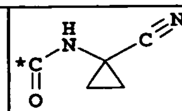
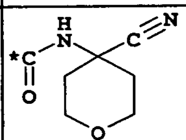
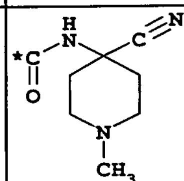
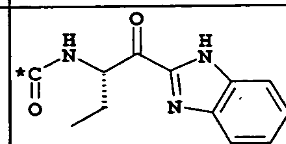
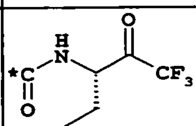
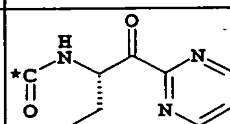
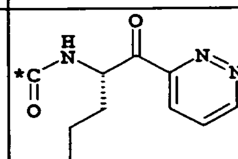
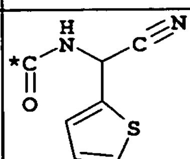
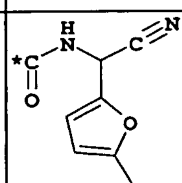
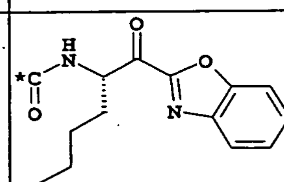
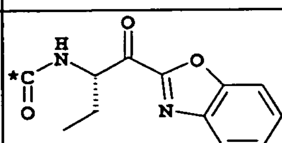
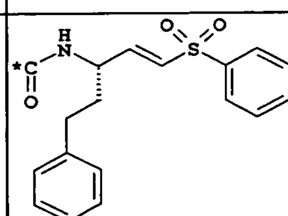
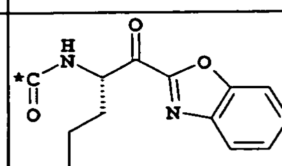
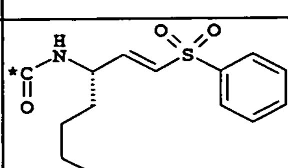
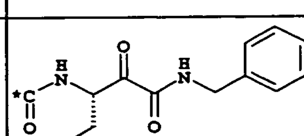
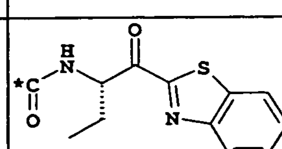
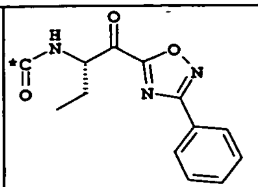
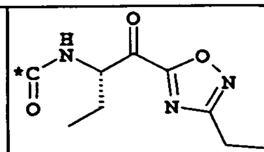
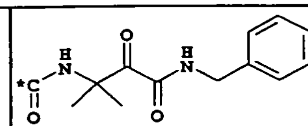
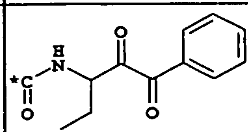
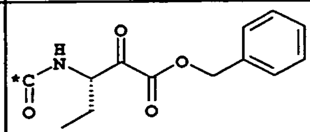
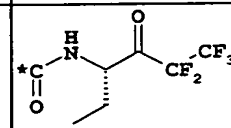
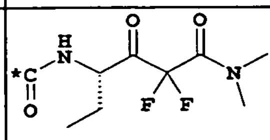
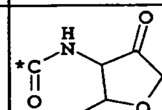
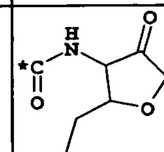
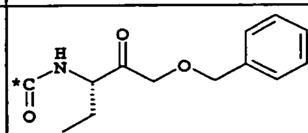
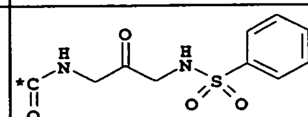
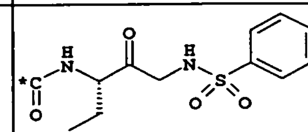
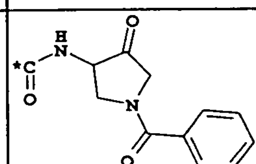
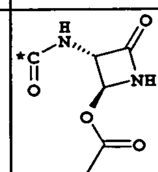
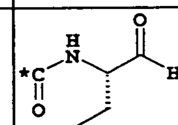
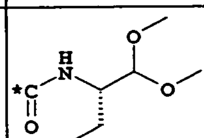
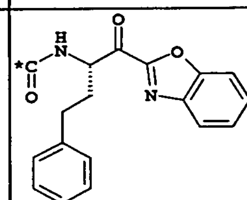
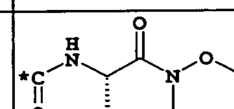
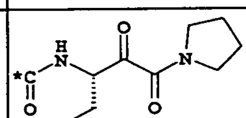
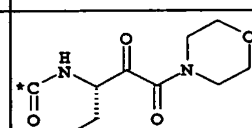
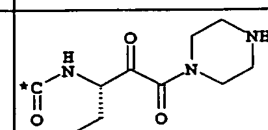
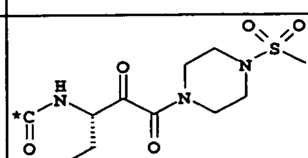
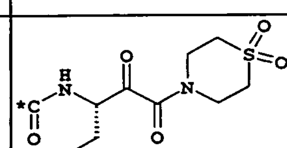
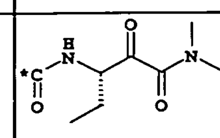
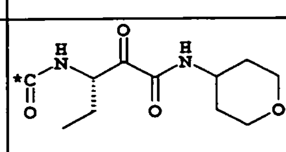
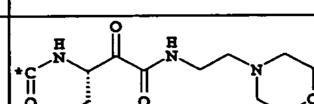
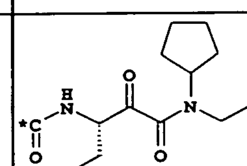
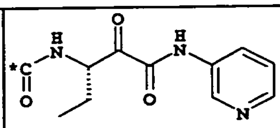
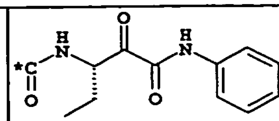
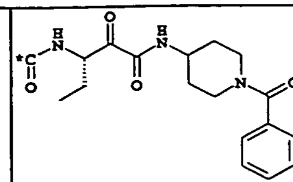
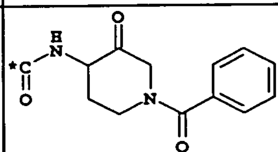
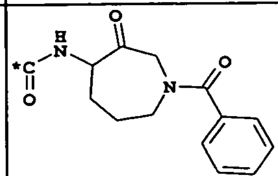
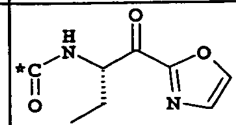
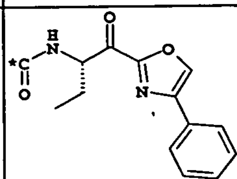
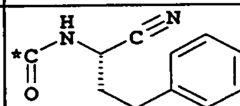
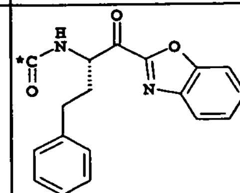
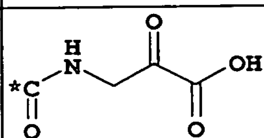
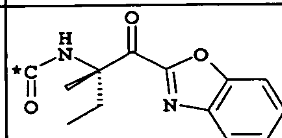
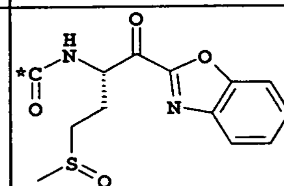
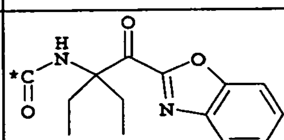
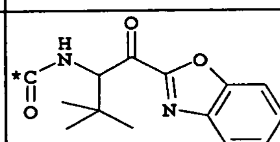
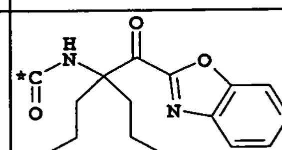
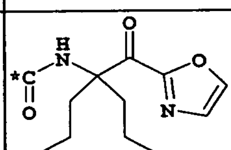
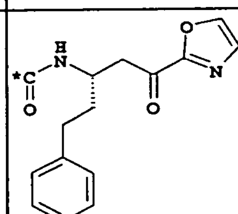
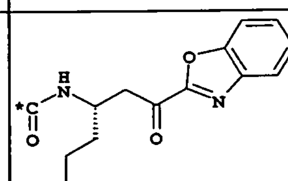
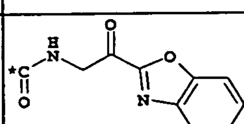
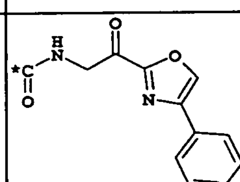
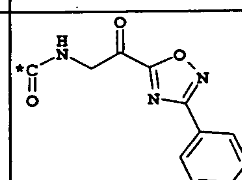
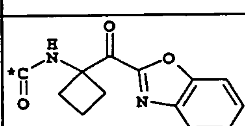
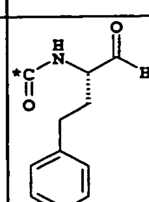
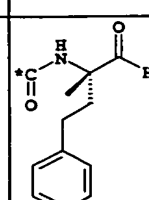
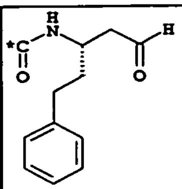
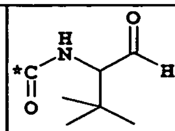
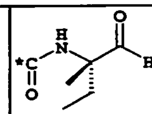
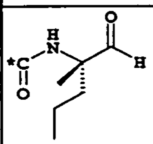
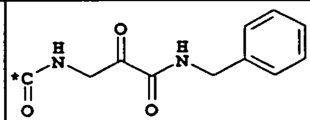
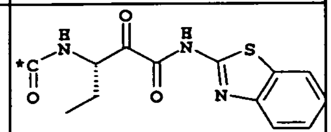
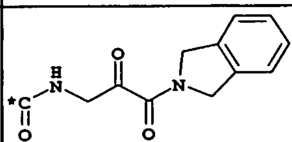
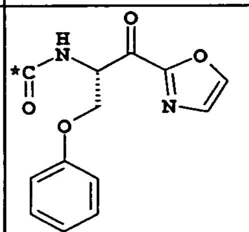
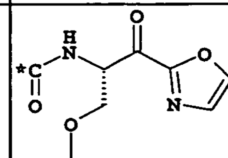
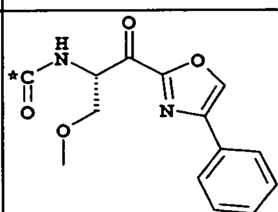
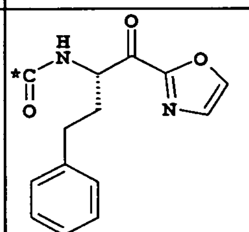
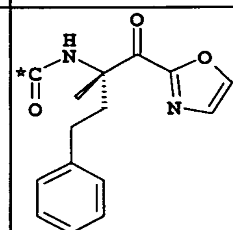
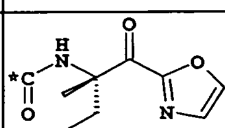
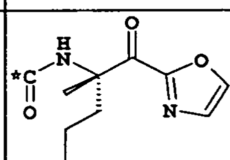
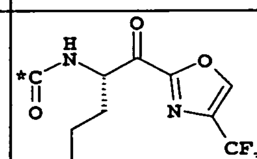
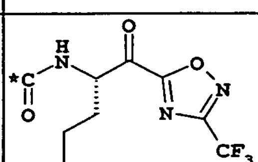
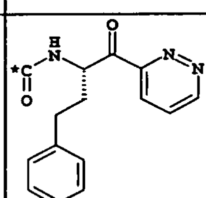
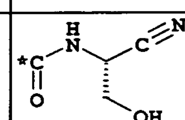
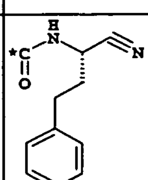
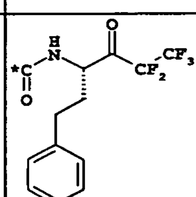
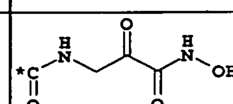
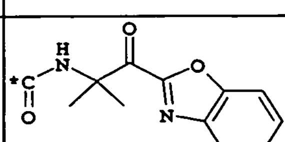
B91		**B92**		**B93**	

TABLE 3

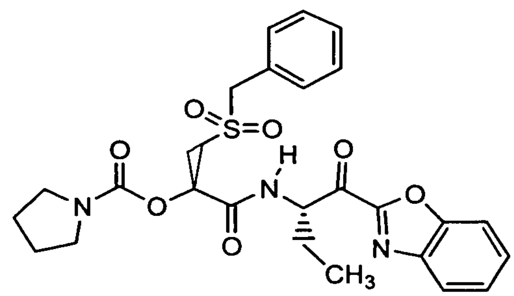
C1		**C2**		**C3**	
C4		**C5**		**C6**	
C7		**C8**		**C9**	
C10		**C11**		**C12**	
C13		**C14**		**C15**	
C16		**C17**		**C18**	

C19		**C20**		**C21**	
C22		**C23**		**C24**	
C25		**C26**		**C27**	
C28		**C29**		**C30**	
C31		**C32**		**C33**	
C34		**C35**		**C36**	
C37		**C38**		**C39**	
C40		**C41**		**C42**	
C43		**C44**		**C45**	

C46		C47		C48	
C49		C50		C51	
C52		C53		C54	
C55		C56		C57	
C58		C59		C60	
C61		C62		C63	
C64		C65		C66	
C67		C68		C69	

C70		C71		C72	
C73		C74		C75	
C76		C77		C78	
C79		C80		C81	
C82		C83		C84	
C85		C86		C87	
C88		C89		C90	
C91					

For convenience, compounds of the present invention may be referenced to by their "A", "B", and "C" fragment combinations. Thus, for example, the compound referenced as A7-B4-C13 is the product of the combination of group A7 in Table 1 and B4 in Table 2 and C13 in Table 3, namely pyrrolidine-1-carboxylic acid (R)-1-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester:



Further preferred compounds of Formula I are provided in the following:

(*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide;

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide;

(*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide;

(*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide;

morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

(R)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

(S)-diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-2-hydroxymethyl-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl

ester;

(S)-(2-hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(Tetrahydrofuran-2-ylmethyl)-carbamic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-(2-methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(R)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester;

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester;

pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester;

(S)-2-{(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino}-*N*-methoxy-*N*-methyl-butyramide;

(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-*N*-((S)-1-formyl-propyl)-2-hydroxy-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide;

(S)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide;

N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionamide;

N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-*p*-tolylmethanesulfonyl-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-116-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)-amide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)-amide;

3-[3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide;

(R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-

phenylmethanesulfonyl-propionamide;

N-[1-(benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide.

(R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide;

(2S) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide;

N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide;

N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide;

N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide;

N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide;

N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide;

N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide;

2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide;

N-(1-(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide;

2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide;

N-(4-cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide;

N-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide;

(S)-tert-butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(R)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester;

(S)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester;

(R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

(R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester;

3-cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide;

(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide;

(S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide;

(S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide;

(R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide;

(1S)-N-[1-(benzooxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide;

2,2-difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide;

morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester;

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester;

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester;

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester;

morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl ester;

4-[4,4-dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide;

(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide;

(R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-

ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;

((R)-2-cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester;

((R)-2-cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester;

{(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

{(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester;

(R)-2-phenylmethanesulfonyl-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester;

(R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide;

(S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide;

S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide;

(R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide;

N-cyanomethyl-3-cyclohexyl-propionamide;

N-cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide;

3-(3-cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide;

3-cyclohexyl-*N*-(1-formyl-3-phenyl-propyl)-propionamide;

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-propionamide;

N-[(S)-1-(benzooxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide;

N-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide;

2-benzyloxy-*N*-cyanomethyl-3-cyclohexyl-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide;

(*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide;

(*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(S)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide;

(*S*)-3-((*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino)-2-oxo-pentanoic acid benzylamide;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide;

(*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide;

(2R,5S)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-morpholin-3-one;and their corresponding N-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their N-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Pharmacology and Utility:

The compounds of the invention are selective inhibitors of cathepsin S and, as such, are useful for treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders, including, but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S also is implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth in ENZYME ASSAY EXAMPLES, *infra*.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from about 1 microgram per kilogram body weight (□g/kg) per day to about 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 □g/kg/day to about 20 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 80□g/day to about 4.8g /day, typically from about 80 □g/day to about 1.6 g/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will

be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 15, *infra*.

Chemistry:

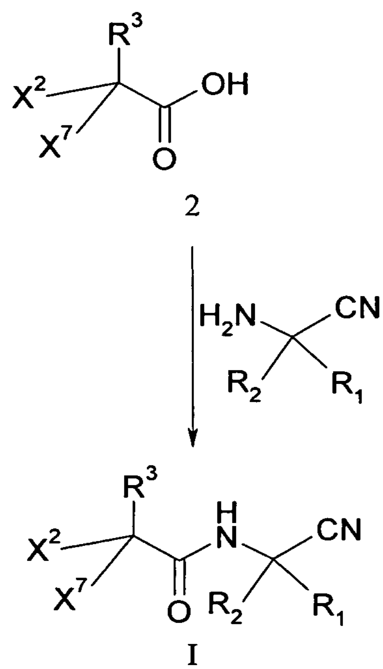
Processes for Making Compounds of Formula I:

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Compounds of Formula I, where X^1 is $-NHC(R^1)(R^2)X^3$, can be prepared by proceeding as in the following Reaction Scheme 1:

Reaction Scheme 1



in which each X^2, X^3, X^7, R^1, R^2 and R^3 are as defined for Formula I in the Summary of the Invention.

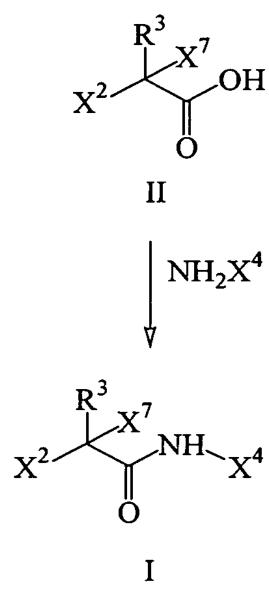
Compounds of Formula I can be prepared by condensing an acid of Formula II with an amino compound of formula $NH_2CR^1R^2X^3$. The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), tetra-methyluroniumhexafluorophosphate (HATU),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), N-cyclohexylcarbodiimide, N'-methylpolystyrene, or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotrizol-1-yl)-1,1,3,3, , or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone®, metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete. Detailed descriptions for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 are set forth in the Examples 1 to 10, *infra*.

Compounds of Formula I, where X^1 is $-NHX^4$, can be prepared by proceeding as in the following Reaction Scheme 2:

Reaction Scheme 2



in which each X^2, X^4, X^7 and R^3 are as defined for Formula I in the Summary of the Invention.

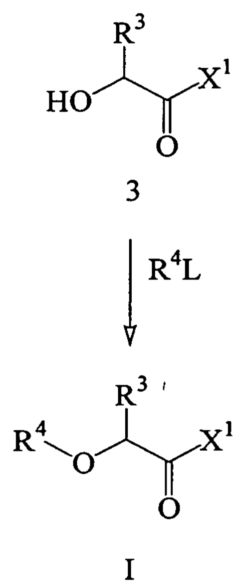
Compounds of Formula I can be prepared by condensing an acid of Formula II with an amino compound of formula NH_2X^4. The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), *O*-(7-azabenzotrizol-1-yl)-1,1,3,3, tetra-

methyluroniumhexafluorophosphate (HATU), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), N-cyclohexylcarbodiimide, N'-methylpolystyrene, or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 5 to 10 hours to complete.

An oxidation step, if required, can be carried out with an oxidizing agent (e.g., Oxone®, metachloroperbenzoic acid or the like) in a suitable solvent (e.g., methanol, water, or the like, or any suitable combination thereof) at ambient temperature and requires 16 to 24 hours to complete.

Compounds of Formula I in which X^2 is $-OR^4$, can be prepared by reacting a compound of Formula 3 with a compound of Formula R^4L according to the following reaction scheme:

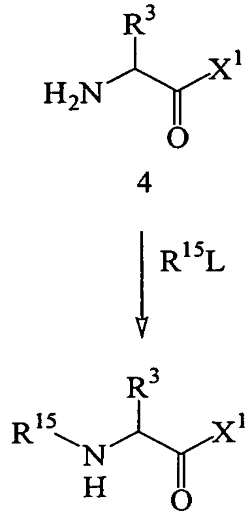
Reaction Scheme 3



in which L is a leaving group and X^1, R^3 and R^4 are as defined in the Summary of the Invention. A detailed description for the synthesis of a compound of Formula I by the process described above is set forth in Example 4, *infra.*

Compounds of Formula I, in which X^2 is $-NHR^{15}$, can be prepared by reacting a compound of Formula 4 with a compound of Formula $R^{15}L$ according to the following reaction scheme:

Reaction Scheme 4



I

in which L is a leaving group and X^1, R^3 and R^{15} are as defined in the Summary of the Invention. A detailed description for the synthesis of a compound of Formula I by the process described above is set forth in [update], *infra.*

Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the

like). A compound of Formula I in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

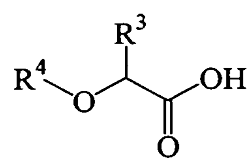
Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diasteromeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline

diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

In summary, the compounds of Formula I are made by a process which comprises:

(A) reacting a compound of Formula II:

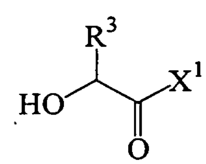


II

with a compound of the formula $NH_2CR^1R^2X^3$, in which X^3, R^1, R^2, R^3 and R^4 are as defined in the Summary of the Invention for Formula I; or

(B) reacting a compound of Formula II with a compound of the formula NH_2X^4, in which X^4, R^3 and R^4 are as defined in the Summary of the Invention for Formula I; or

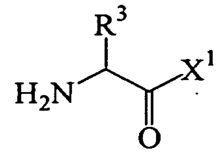
(C) reacting a compound of Formula 3:



3

with a compound of formula R^4L, in which X^1, R^3 and R^4 are as defined in the Summary of the Invention and L is a leaving group; or

(D) reacting a compound of Formula 4:



4

with a compound of formula $R^{15}L$, in which X^1, R^3 and R^4 are as defined in the Summary of the Invention and L is a leaving group; and

(E) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(F) optionally converting a salt form of a compound of Formula I to non-salt form;

(G) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(H) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;

(I) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(J) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(K) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

Examples:

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula I and II (Examples) and intermediates (References) according to the invention.

LC/MS-Procedures:

LC/MS (Method A):

Mass Spectrometer (MS) - LCT Time-of-Flight (Micromass UK Ltd) Serial No. KA014

Ionization Mode: Electrospray (Positive Ion)

Scan: Tof MS (Full Scan m/z 100 - 1200, sum for 0.4 s @ 50us/scan) Centroid Mode

Liquid Chromatograph (LC): Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343)

& Degasser (serial # JP73008973)

Mobile Phase:

A = Water + 0.05% TFA (trifluoroacetic acid) buffer

B = Acetonitrile + 0.05% TFA buffer

Gradient: 5%B to 100%B in 5 minutes

Column: Hypersil BDS C-18, 3u, 4.6mm x 50mm Reverse Phase

Injection volume: 5 uL

Flow rate: 1ml/min to column & to UV detector, flow split after UV detector such that 0.75ml/min to ELS detector and 0.25ml/min to mass spectrometer.

Auxiliary Detectors: (i) Hewlett Packard Model HP1100 Series UV detector (serial # JP73704703) wavelength = 220nm

(ii) Sedere (France) Model SEDEX 75 Evaporative Light Scattering (ELS) detector (serial # 9970002A)

temperature = 46 deg C, Nitrogen pressure = 4bar

Autosampler / Injector: Gilson Model 215 Liquid Handler with Model 819 injection valve (serial # 259E8280)

LC/MS (Method B):

Same as method A, but with a different gradient: 5%B to 90%B in 3 minutes, 90%B to 100%B in 2 min

LC/MS (Method C):

Mass Spectrometer (MS) - LCT Time-of-Flight (Micromass UK Ltd) Serial No. KA014

Ionization Mode: Electrospray (Positive Ion)

Scan: Tof MS (Full Scan m/z 100 - 1200, sum for 0.4 s @ 50us/scan) Centroid Mode

Liquid Chromatograph (LC): Hewlett Packard HP1100 Series Binary Pump (Serial # US80301343)

& Degasser (serial # JP73008973)

Mobile Phase:

A = Water + 0.1% formic acid buffer

B = Acetonitrile + 0.1% formic acid buffer

Gradient: 5%B to 90%B in 3 minutes, 90%B to 100%B in 2 min

Column: Phenomenex Synergi C-18, 2u, 4.mm x 20mm Reverse Phase
Injection volume: 5 uL
Flow rate: 1ml/min to column & to UV detector, flow split after UV detector such that 0.75ml/min to ELS detector and 0.25ml/min to mass spectrometer.

Auxiliary Detectors: (i) Hewlett Packard Model HP1100 Series UV detector (serial # JP73704703) wavelength = 220nm

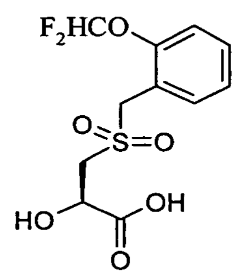
(ii) Sedere (France) Model SEDEX 75 Evaporative Light Scattering (ELS) detector (serial # 9970002A)

temperature = 46 deg C, Nitrogen pressure = 4bar

Autosampler / Injector: Gilson Model 215 Liquid Handler with Model 819 injection valve (serial # 259E8280)

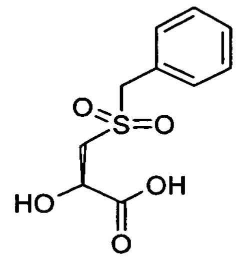
REFERENCE EXAMPLE 1

(a) (R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid



A solution of (R)-2-*tert*-Butoxycarbonylamino-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid (5.19g) in CH_2Cl_2 (20mL), was treated with trifluoroacetic acid (20mL) at room temperature. After two hours, the reaction mixture was concentrated under reduced pressure. The white solid obtained was dissolved in 1M H_2SO_4 (100mL) and dioxane (30mL). The solution was cooled to 0°C, $NaNO_2$ (1.95g in 50mL of water) was added with stirring for 1 hour. The reaction mixture was stirred overnight at ambient temperature. The product was then concentrated and extracted with ethyl acetate, dried with anhydrous $MgSO_4$, filtered, concentrated and recrystallized from ethyl acetate to yield (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid (2.36g).

(b) (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid



By proceeding in a manner similar to Reference Example 1(a) above but using (R)-2-*tert*-butoxycarbonylamino-3-[phenylmethanesulfonyl]-propionic acid there was prepared (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid.

REFERENCE EXAMPLE 2

(R)-2-Amino-*N*-methoxy-*N*-methyl-butyramide

To a solution of [(R)-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid *tert*-butyl ester (4.92g, 20mmol) in CH_2Cl_2 (20ml) was added TFA (10mL) at room temperature. After stirring for 2 hours, the reaction mixture was concentrated to dryness under reduced pressure to produce (R)-2-amino-*N*-methoxy-*N*-methyl-butyramide TFA salt (5.4g).

REFERENCE EXAMPLE 3

(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-triisopropylsilanyloxy-propionic acid

(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid (7.0g, 22.58mmol), in CH_2Cl_2 (50mL) was reacted with 2, 6-lutidine (12.09g, 112.9mmol) and triisopropylsilyl-trifluoro-methanesulfonate (20.75g, 67.74mmol) at -78°C for one hour. The reaction mixture was allowed to warm to room temperature before being quenched by the addition of saturated ammonium chloride solution. The product was extracted with ethyl acetate, the solvent was removed under reduced pressure and the oil residue was then dissolved in EtOH:THF:H_2O (3:1:1, 60mL). Solid K_2CO_3 (24g) was added at room temperature and the mixture was stirred for one hour, filtered, extracted with ethyl acetate, dried with anhydrous $MgSO_4$, filtered and concentrated to yield (R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-triisopropylsilanyloxy-propionic acid (8.58g).

Following as in reference 3 provided the following intermediate:

(R)-3-Phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionic acid

REFERENCE EXAMPLE 4

3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid

A mixture of [2-(1,1-difluoro-methoxy)-phenyl]-methanethiol (190mg, 1.0mmol), acrylic acid (69□L, 1.0mmol), diisopropylethylamine (44□L, 1.1mmol) and 0.5mL dimethylformamide was stirred at 45^{O}C for 4 hours. Diethyl ether (5mL) and 1N HCl (2mL) was added. The layers were separated and the organic layer was washed with 1N HCl (2mL), dried over $MgSO_4$ and concentrated. The resulting oil was dissolved in methanol (5mL), treated with an aqueous solution (5mL) of Oxone® (921mg, 1.5mmol), and stirred for 1 hour. Methanol was removed under reduced pressure and 20mL water was added. The mixture was extracted with two 60mL portions of ethyl acetate, dried over $MgSO_4$ and concentrated to give 3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid (160mg; 0.54mmol, 54% yield).

REFERENCE EXAMPLE 5

3-Benzylsulfanyl-2-(2-nitro-phenylamino)-propionic acid

S-benzylcysteine (1.06g, 5.0mmol), 2-fluoronitrobenzene (1.05mL, 10.0mmol), potassium carbonate (1.38g, 10.0mmol) and dimethylformamide (3mL) were combined and stirred at 100°C for 4 hours. The mixture was diluted with 40mL water and washed with two 15mL portions of diethyl ether. The aqueous layer was acidified to pH 4 with 6N HCl and extracted with two 30mL portions of ethyl acetate. The ethyl acetate layer was dried over $MgSO_4$, and concentrated. Diethyl ether was added and then decanted to give 3-benzylsulfanyl-2-(2-nitro-phenylamino)-propionic acid (541mg, 1.63mmol, 33%yield).

REFERENCE EXAMPLE 6

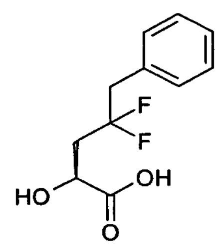
(R)-3-Benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid

S-benzylcysteine (0.845g, 4mmol) and bis(trimethylsilyl)acetamide (3mL, 16mmol) were stirred at 75^{O}C for 1 hour. 2-Bromo-5-nitrothiazole (837mg, 4mmol) and toluene (8mL) was added and the mixture was stirred at 100^{O}C for 1 day. Toluene was removed under reduced

pressure. The residue was stirred in 5mL dioxane and 5mL 1N HCl for 30 minutes. Dioxane was removed under reduced pressure and the mixture was basified with saturated $NaHCO_3$ and washed with 50mL ethyl acetate. The aqueous layer was acidified with 6N HCl and extracted with two 25mL portions of ethyl acetate, dried over $MgSO_4$, concentrated and chromatographed using a gradient of 5-10% methanol in methylene chloride to yield (R)-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid (42.7mg, 0.123mmol, 3% yield).

REFERENCE EXAMPLE 7

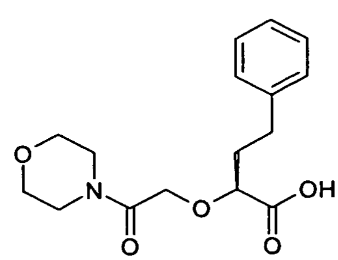
(2S)-4,4-Difluoro-2-hydroxy-5-phenyl-pentanoic acid



To a suspension of (S)-2-Amino-4,4-difluoro-5-phenyl-pentanoic acid (1.0 mmol, 230mg) in water (3mL) was added 2M sulfuric acid dropwise until the solid dissolved (ca 3mL). A solution of sodium nitrite (1.5 eq., 1.5 mmol, 104mg) in 1 ml of water was then added dropwise. The mixture was stirred at room temperature for 21 hours then extracted twice with ether (30 ml). The organic layers were dried over MgSO4 and then concentrated in vacuum to afford (2S)-4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (90 mg, 39%) as a white solid. ^{1}H NMR ($CDCl_3$) 7.3 (m, 5H), 5.6 (b, 1H), 4.61 (dd, J=8.5, 2.9 Hz, 1H), 3.3 (t, J=16.8 Hz, 2H), 2.45 (m, 1H), 2.2 (m, 2H).

REFERENCE EXAMPLE 8

2-(S)-(2-Morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid



Step (i): To a cooled (0°C) solution of ethyl (2R) 2-hydroxy-4-phenylbutyrate (1.81g, 8.71 mmol), 4-nitro-benzoic acid (1.1eq., 9.56 mmol,1.598g) and triphenyl phosphine (1.1 eq., 9.5 mmol, 2.50g) in dry THF (80mL) under nitrogen was added slowly diethyl azodicarboxylate

(1.1 eq., 9.56 mmol, 1.67g). The mixture was stirred at 0°C for 2.5 hours and then concentrated in vacuum. The residue was triturated with a mixture of ethyl acetate and heptane (1:3, 150mL) and the resulting solids were filtered off. The filtrate was concentrated in vacuum and purified over 110g silica gel, eluting with a mixture of ethyl acetate and heptane (1:4, v/v) to afford 4-nitro-benzoic acid (S)-1-ethoxycarbonyl-3-phenyl-propyl ester (3.4g, 98%).

Step (ii): To a cooled (0°C) solution of 4-nitro-benzoic acid (S)-1-ethoxycarbonyl-3-phenyl-propyl ester (2.04 g, 5.83 mmol) in MeOH (30 mL) was added potassium carbonate (1.5 eq., 8.75 mmol, 1.21g). The mixture was stirred at 0°C for 5 minutes then at room temperature for 1.5 hours and concentrated in vacuum. The residue was partitioned between water (40mL) and ethyl acetate (40mL). The organic layer was dried over MgSO4 and then concentrated in vacuum. The residue was purified over 35g silica gel, eluted with dichloromethane to afford methyl-(2S)-2-hydroxy-4-phenyl-butyrate as a colorless oil (933mg, 82%).

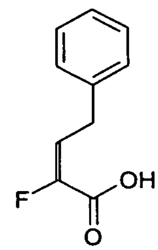
Step (iii): To a solution of methyl-(2S)-2-hydroxy-4-phenyl-butyrate (300mg, 1.54 mmol) in dry DMF (3mL) under nitrogen was added sodium hydride (60%, 1.5 eq., 2.32 mmol, 92.7mg). After 5 min, 4-(2-chloroacetyl) morpholine (1.1 eq., 1.69 mmol, 277mg) was added and the mixture was stirred at room temperature for 24 hours, then diluted with water (60mL) and then neutralized with 1 N HCl. The aqueous solution was extracted twice with ethyl acetate (40mL). The organic layer was washed with water (50mL), dried over MgSO4 and then concentrated in vacuum. The residue was purified over 35g silica gel, eluting with ethyl acetate then with 5% MeOH in ethyl acetate to afford (S)-2-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid methyl ester (117mg, 24%).

Step (iv): To a solution of (S)-2-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid methyl ester (117mg, 0.36 mmol) in MeOH:H_2O (2:1 vol, 3mL) was added lithium hydroxide hydrate (2.0 eq., 0.73 mmol, 30.5mg). The mixture was stirred at room temperature for 5 hours, then diluted with water (30mL) and then extracted with ether (30mL). The aqueous layer was acidified with 1N HCl and extracted twice with ether (30mL). The acidic extracts were dried over $MgSO_4$ and then concentrated in vacuum to afford (S)-2-(2-Morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid (85.5mg, 77%) as a colorless oil. ^1H NMR ($CDCl_3$) 10.5 (b, 1H), 7.2 (m, 5H), 4.55 (d, J=15.2 Hz, 1H), 4.14 (d, J=15.2 Hz, 1H), 3.9 (dd, J=7.6, 4.2 Hz,

1H), 4.6 (m, 6H), 3.4 (m, 2H), 2.8 (m, 2H), 2.3 (m, 1H), 2.15 (m, 1H). LC/MS 96% (M+1) 308.

REFERENCE EXAMPLE 9

(2S)-2-Fluoro-4-phenyl-butyric acid

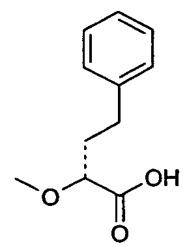


Step (i): To a cooled (0°C) solution of methyl-(2R)-2-hydroxy-4-phenyl-butyrate (1.00g, 4.80 mmol) in dry dichloromethane (3mL) was added DAST (3.0eq., 14.4 mmol, 2.32g). The mixture was stirred at room temperature for 18 hours then diluted with dichloromethane (20mL) and carefully quenched with saturated sodium bicarbonate (150mL). The aqueous layer was extracted with dichloromethane (30mL) and the organic layers were dried over MgSO4 and then concentrated in vacuo. The residue was purified over 90g silica gel, eluting with a mixture of dichloromethane and heptane (1:2 then 1:1, v/v) to afford methyl-2S-fluoro-4-phenyl-butyrate as a light yellow oil (578 mg, 57%).

Step (ii): To a solution of methyl-2S-fluoro-4-phenyl-butyrate (577mg, 2.74 mmol) in a mixture of MeOH:H2O (2:1 vol, 6mL) was added lithium hydroxide monohydrate (1.5 eq., 4.11 mmol, 173mg). The mixture was stirred at room temperature for 5 hours and then concentrated in vacuum. The residue was diluted with water (30mL) and extracted with ether (20mL). The aqueous layer was acidified with HCl and extracted with ether (30mL). The acidic extract was dried over MgSO4 and then concentrated in vacuum to afford 2(S)-fluoro-4-phenyl-butyric acid as a yellow oil (486 mg, 97%). ^{1}H NMR ($CDCl_3$) 7.5 (b, 1H), 7.3 (m, 5H), 4.95 (ddd, J=48.9, 6.9, 5.4 Hz, 1H), 2.85 (m, 2H), 2.25 (m, 2H). MS (CI) M+1 183.

REFERENCE EXAMPLE 10

2(R)-Methoxy-4-phenyl-butyric acid



Step 1: To a solution of ethyl-(2R)-2-hydroxy-4-phenyl-butyrate (500mg, 2.40 mmol) in dry DMF (4mL) under nitrogen was added sodium hydride (60%, 2.0 eq., 4.80 mmol, 192mg) followed by methyl iodide (3.0 eq., 7.20 mmol, 1.02g). The mixture was stirred at room temperature for 22 hours, then diluted with NH_4Cl (100mL) and extracted with ethyl acetate (50mL). The organic layer was dried over MgSO4 and then concentrated in vacuum. The residue was purified over 35g silica gel, eluting with ethyl acetate and heptane (1:3, v/v) to afford (R)-2-methoxy-4-phenyl-butyric acid ethyl ester(480 mg, 90%).

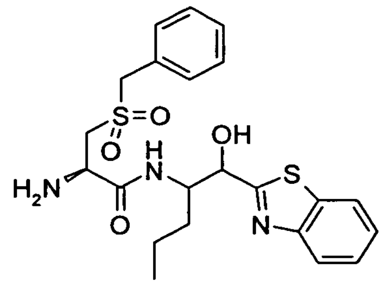
Step 2: To a solution of (R)-2-methoxy-4-phenyl-butyric acid ethyl ester (480mg, 2.8 mmol) in MeOH:H_2O (2:1 vol, 9mL) was added lithium hydroxide hydrate (2.0 eq., 4.32 mmol, 181mg). The mixture was stirred at room temperature for 2.5 hours, then diluted with water (20mL) and then extracted with ether (20mL). The aqueous layer was acidified with 1N HCl and then extracted twice with ether (30 mL). The combined extracts were dried over MgSO4 and then concentrated in vacuum to afford 2(R)-methoxy-4-phenyl-butyric acid (426mg, quant.) as a colorless solid. ^{1}H NMR ($CDCl_3$) 7.25 (m, 5H), 3.8 (dd, J=6.8, 5.2 Hz, 1H), 3.48 (s, 3H), 2.78 (t, J=7.3 Hz, 2H), 2.1 (m, 2H). MS (CI) M 194.

Following as in reference 10 but using benzyl bromide in step 2 provided the following intermediate:

2(R)-Benzyloxy-4-phenyl-butyric acid

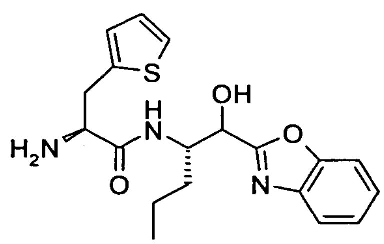
REFERENCE EXAMPLE 11

(a) (R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



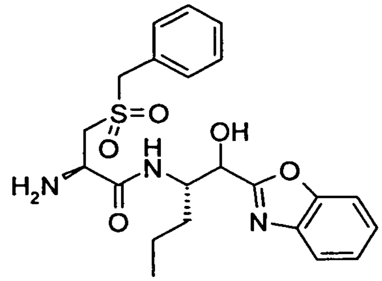
A solution of {(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {888mg, 1.58mmol, Example 27(a)} in dichloromethane (5mL) was treated with trifluoroacetic acid (5mL). The mixture was stirred at room temperature for one hour and then evaporated. The residue was dissolved in dichloromethane (20mL) and this solution was treated with Silicycle Triamine (4.3g, 16mmol). The mixture was stirred at room temperature for two hours and then filtered. The filtrate was evaporated to give the title compound (692mg, 94%). LC/MS m/z=562 (M+H).

(b) (S)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide



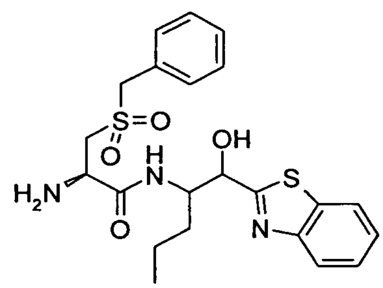
By proceeding in a manner similar to Reference Example 11(a) above but using {(S)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester {790mg, 1.67mmol, Example 27(c)} and subjecting the reaction product to flash chromatography on silica eluting with a mixture of ethyl acetate and methanol (9:1, v/v) there was prepared (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide (415mg, 66%). LC/MS m/z=374 (M+H).

(c) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



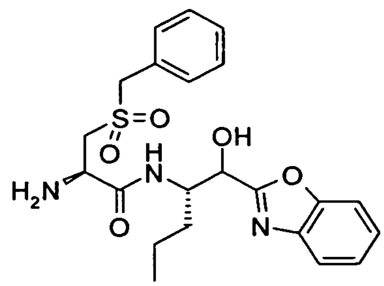
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {908mg, 1.66mmol, Example 27(b)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (726mg, 98%). LC/MS m/z=446 (M+H).

(d) (R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



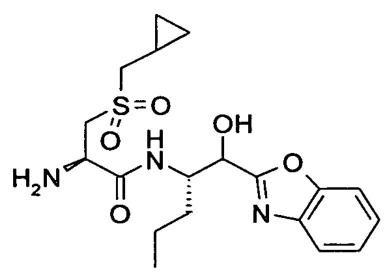
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {0.63mmol, Example 27(d)} there was prepared (R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (212mg, 73%). LC/MS m/z=462 (M+H).

(e) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



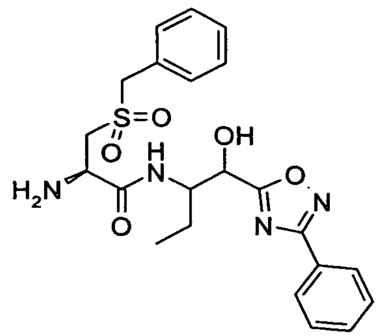
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {1.7mmol, Example 27(e)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide (726mg, 98%). LC/MS m/z=446 (M+H).

(f) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide



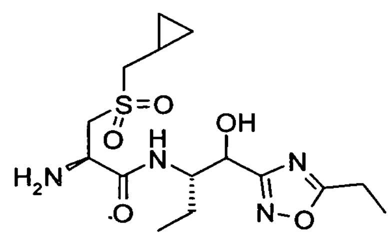
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {450mg, 0.88mmol, Example 27(f)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide (360mg, 0.879mmol, 100%).
LC/MS m/z=410(M+H)

(g) (R)-2-Amino-N-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-3-phenylmethanesulfonyl-propionamide



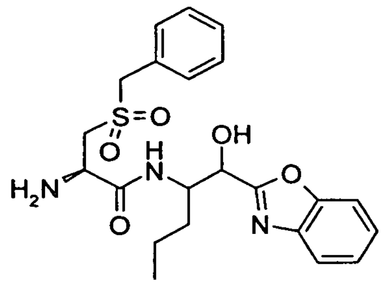
By proceeding in a manner similar to Reference Example 11(a) above but using (R)-1-{1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester {Example 27(g)} there was prepared (R)-2-amino-N-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-3-phenylmethanesulfonyl-propionamide. LC/MS m/z=481 (M+Na), 459(M+H)

(h) (R)-2-Amino-3-cyclopropylmethanesulfonyl-N-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-propionamide



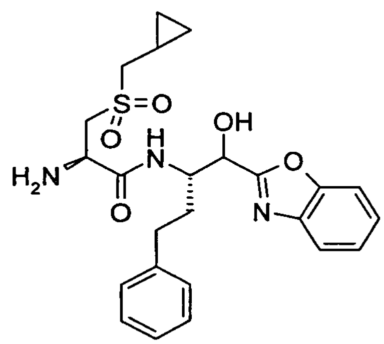
By proceeding in a manner similar to Reference Example 11(a) above but using ((R)-2-cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester {Example 27(i)} there was prepared (R)-2-amino-3-cyclopropylmethanesulfonyl-N-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-propionamide. LC/MS m/z=375(M+H)

(i) (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide



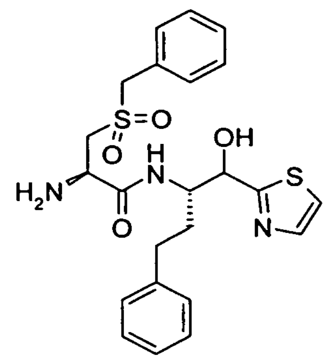
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {Example 27(j)} there was prepared (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide. LC/MS m/z=446(M+H)

(j) (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-propionamide



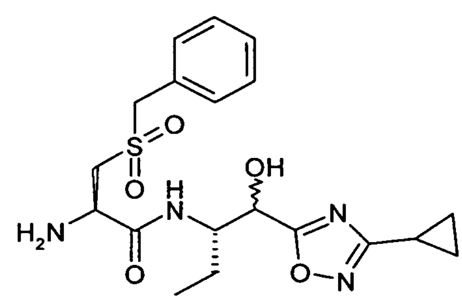
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {Example 27(k)} there was prepared (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-propionamide. LC/MS m/z=472(M+H)

(k) (R)-2-Amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide



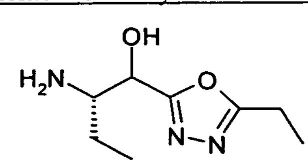
By proceeding in a manner similar to Reference Example 11(a) above but using {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester {Example 27(l)} there was prepared (R)-2-amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide.

(l) (R)-2-Amino-3-phenylmethanesulfonyl-N-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-propionamide



By proceeding in a manner similar to Reference Example 11(a) above but using ((R)-2-phenylmethanesulfonyl-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester {Example 27(s)} there was prepared (R)-2-amino-3-phenylmethanesulfonyl-N-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-propionamide.

(m) 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl-butan-1-ol

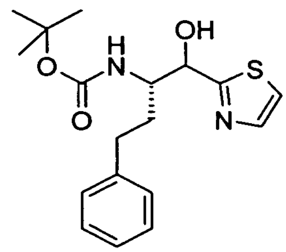


By proceeding in a manner similar to Reference Example 11(a) above but using {1-[(5-ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid *tert*-butyl ester (Reference

Example 16) there was prepared 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl-butan-1-ol.

REFERENCE EXAMPLE 12

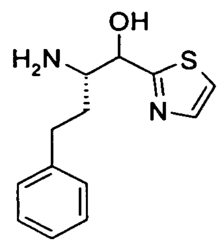
[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester



n-Butyllithium (4.2ml, 10.5mmol, 2.5M solution in hexanes) was mixed with 16ml diethylether and the resulting solution cooled to –78^{0}C. 2-Bromothiazole (1.64g, 10mmol) was dissolved in a mixture of 2ml diethylether and 1ml THF. This solution was added dropwise to the n-butyllithium solution. The resulting reaction mixture was stirred for 15min. A solution of [(S)-1-(Methoxy-methyl-carbamoyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (1.4g, 4.3mmol) in 20ml THF was added dropwise to the reaction mixture. Stirring was continued for one hour and the reaction mixture quenched by addition of 50ml water. After warming to room temperature the phases were separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvents were evaporated under vacuum to give 1.4g [(S)-3-Phenyl-1-(thiazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester as a brown solid. [(S)-3-Phenyl-1-(thiazole-2-carbonyl)-propyl]-carbamic acid tert-butyl ester (1.41g, 4.1mmol) was dissolved in 50 ml ethanol and the solution cooled to 0^{0}C. Sodium borohydride (155mg, 4.1mmol) was added and the reaction mixture stirred for 90 minutes. Water was added and the aqueous phase acidified by addition of 1M hydrochloric acid. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure. (1.32, 3.8mmol, 88%). LC/MS m/z=271 (M+H-isobutene), 249(M+H-boc)

REFERENCE EXAMPLE 13

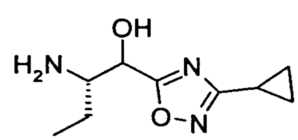
(S)-2-Amino-4-phenyl-1-thiazol-2-yl-butan-1-ol



[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (1.32g, 3.8mmol, Reference Example 12) was dissolved in 10ml dichloromethane. Trifluoroacetic acid was added and the resulting reaction mixture stirred for two hours. The solvents were evaporated under reduced pressure and saturated sodium bicarbonate solution was added. The solution was extracted with ethyl acetate. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent was evaporated and the crude product purified via flash chromatography (eluted with ethyl acetate followed by 10% methanol in ethyl acetate) to give <u>(S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol</u> (466mg, 1.87mmol, 49%). LC/MS m/z=249(M+H).

REFERENCE EXAMPLE 14

<u>(S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol</u>



A solution of boc-3S-amino-2-hydroxypentanoic acid (2.00g, 8.57mmol) and 1.20 equivalents of cyclopropanecarboxamidoxime (1.03g, 10.29mmol) in 20 mL of dichloromethane was stirred at 0°C as 1.25 equivalents of N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.70mmol/g, 6.30g, 10.72mmol) was added in portions and the reaction mixture stirred under nitrogen for three hours while warming to 15°C. The reaction mixture was filtered and the resin washed with dichloromethane. Evaporate under vacuum to dryness. [LC/MS m/z=338 (M+H+Na)] The residue is dissolved in 20 mL of tetrahydrofuran and heated in a microwave reactor at 160°C for three minutes. Evaporate under vacuum to dryness. [LC/MS m/z=320 (M+H+Na)] The residue is dissolved in 50 mL of dichloromethane and stirred at room temperature as a 50 mL solution of 50% trifluoroacetic acid in dichloromethane was added dropwise. After three hours the reaction was evaporated under vacuum to dryness and dissolved in 50 mL of dichloromethane again. Three equivalents of Silicycle triamine-3 was added and the mixture stirred at room temperature overnight. The mixture was filtered and

washed with dichloromethane. Evaporate under vacuum to give (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol 1.04g (61% overall). [LC/MS m/z=198 (M+H)]

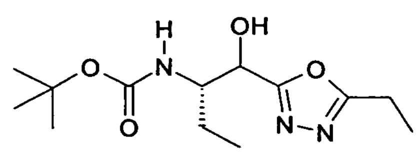
REFERENCE EXAMPLE 15

Ethyl-1,3,4-oxadiazole:

A mixture of the formic hydrazide (60g, 1mole), triethylorthopropionate (176.26g, 1mole) and p-toluenesulfonic acid (250mg) was heated at 120°C for 12 hours. The ethanol was removed under vacuum and the residue was distilled under vacuum to yield 24g of ethyl-1,3,4-oxadiazole. H^1 NMR (DMSO-□): 9.34 (1H, s), 2.86 (2H, q), 1.25(3H, t).

REFERENCE EXAMPLE 16

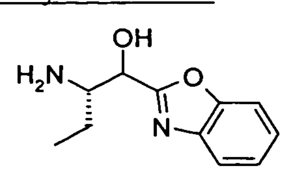
{1-[(5-Ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid *tert*-butyl ester



To a stirred solution of the ethyl-1,3,4-oxadiazole (4.66g, 48mmol, Reference Example 15) in THF (50ml) was added n-BuLi (1.6M solution in 30ml of hexane) drop-wise under N_2 at –78°C. After 1 hour, MgBr∘Et_2O (12.38g, 48mmol) was added and the reaction mixture was allowed to warm to -45°C for 1 hour before being treated with 2-Boc-Nlu-aldehyde (3.2g, 24mmol) in THF (20ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to yield {1-[(5-ethyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid *tert*-butyl ester (2.13g). ^{1} NMR (DMSO-□): 6.65, 6.52(1H, d, d, J=9.2Hz, J=9.2Hz, NH, diastereomer), 6.14, 5.95(1H, d, d, J=5.6Hz, J=5.6Hz, OH, diastereomer), 4.758, 4.467(1H, m, diastereomer), 3.7-3.55(1H, m), 2.8(2H, q), 1.33(12H, t), 1.25-1.21(2H, m), 0.82(3H, m). MS: 284.1 (M-1), 286 (M+1), 308(M+Na).

REFERENCE EXAMPLE 17

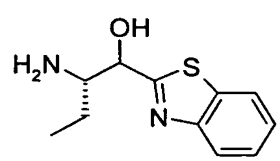
(a) (S)-2-Amino-1-benzooxazol-2-yl-butan-1-ol



Step 1. Benzoxazole (600 mg, 5 mmol) in 20 ml THF was cooled to -5°C and isopropyl magnesium chloride (2M in THF, 2.5 ml, 5 mmol) was added. After stirring for 1 hour at -5°C, (S)-(1-formyl-propyl)-carbamic acid tert-butyl ester {561 mg, 3 mmol, Reference Example 18(a)}, prepared as in reference 15, in 10 ml THF was added. The reaction was allowed to warm to room temperature with stirring for 2 hours. The reaction was quenched with saturated ammonium chloride solution, excess THF solvent removed. The residue was extracted with EtOAc, washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatograph to yield 688 mg product (75%); LC-MS: 305.2 (M-1), 307.0 (M+1).

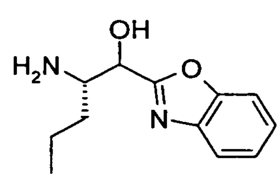
Step 2. (S)-[1-(Benzooxazol-2-yl-hydroxy-methyl)-propyl]-carbamic acid *tert*-butyl ester (275mg, 0.89mmol) and $MeCl_2$ (5ml) were mixed and TFA (1ml) was added at room temperature. After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 260mg of <u>(S)-2-amino-1-benzooxazol-2-yl-butan-1-ol TFA salt</u>.

(b) <u>(S)-2-Amino-1-benzothiazol-2-yl-butan-1-ol</u>



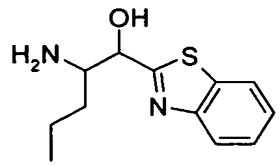
By proceeding in a similar manner to Example 17(a) but using benzothiazole in Step 1 there was prepared <u>(S)-2-amino-1-benzothiazol-2-yl-butan-1-ol TFA salt</u>.

(c) <u>(S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol</u>



By proceeding in a similar manner to Example 17(a) but using (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester {561 mg, 3 mmol, Reference Example 18(b)} in Step 1 there was prepared <u>(S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol</u>.

(d) <u>2-amino-1-benzothiazol-2-yl-pentan-1-ol</u>



By proceeding in a similar manner to Example 17(a) but using benzothiazole and (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester {561 mg, 3 mmol, Reference Example 18(b)} in Step 1 there was prepared 2-amino-1-benzothiazol-2-yl-pentan-1-ol.

REFERENCE EXAMPLE 18

(a) (S)-(1-Formyl-propyl)-carbamic acid tert-butyl ester

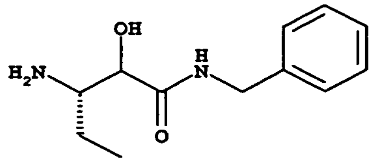
(S)-(+)-2-amino-1-butanol (50g, 561mmol) in 200ml of water and 200ml dioxane was cooled to 0°C and mixed with NaOH (26.9g, 673mmol) and di-t-butyl-dicarbonate (146.96 g, 673mmol). After the addition, the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 2 hours. After removing the dioxane, the residue was extracted with EtOAc, then washed with brine and dried with anhydrous $MgSO_4$, filtered and concentrated. Without further purification, the crude product (120g) was used for next step reaction.

A solution of oxylyl chloride (40.39 g, 265mmol) in 700ml of $MeCl_2$ was stirred and cooled to –60°C. Dimethylsulfoxide (51.7 g, 663mmol) in 100 ml of $MeCl_2$ was added drop wise. After 10 minutes a solution of (S)-2-boc-amino-1-butanol (50 g, 265 mmol) in 100ml of $MeCl_2$ was added drop wise at –70°C. The reaction mixture was allowed to warm to –40°C for 10 minutes and then cooled to –70°C again. A solution of triethylamine (74.9 g, 742mmol) in 100 ml of $MeCl_2$ was added. The reaction mixture was allowed to warm to room temperature over 2 hours. 100mls of saturated sodium dihydrogen phosphate was added, and then the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed to yield 45g of (S)-(1-formyl-propyl)-carbamic acid tert-butyl ester; H^1 NMR (DMSO-□): 9.4(1H, s), 7.29(1H, br.), 3.72(1H, m), 1.69(2H, m), 1.4-1.2(9H, s), 0.86(3H, t).

(b) By proceeding in a similar manner to Reference Example 18(a) but using (S)-(+)-2-amino-1-pentanol there was prepared (S)-(1-formyl-butyl)-carbamic acid tert-butyl ester.

REFERENCE EXAMPLE 19

(S)-3-Amino-2-hydroxy-pentanoic acid benzylamide



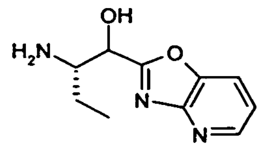
Step1. (1S)-(2-Cyano-1-ethyl-2-hydroxyethyl)carbamic acid tert-butyl ester (10g, 46.7mmol) was dissolved in 1,4-dioxane (100mL). Anisole (5mL) was added and then concentrated HCl (100mL). The mixture was heated under reflux for 24 hours. The mixture was evaporated to dryness under vacuum and re-dissolved in 100mL water. The solution was washed with ether and then neutralized with saturated aqueous $NaHCO_3$. Di-*tert*-butyl dicarbonate (10g, 46mmol) was added with 1,4-dioxane (200mL), and the mixture was stirred at ambient temperature for 24 hours. The dioxane was removed under vacuum and the remaining aqueous solution was washed with ether. The solution was acidified with 1N HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with magnesium sulfate and evaporated to yield 3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (4.5g) as yellowish oil.

Step 2. 3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (300mg, 1.29mmol) was combined with EDC (400mg, 2.1mmol) and HOBt (400mg, 2.6mmol). A solution of benzylamine (0.22mL) and 4-methylmorpholine (0.5mL) in dichloromethyl (4mL) was added in one portion. The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$ solution and brine. The resultant mixture was dried with magnesium sulfate and evaporated under vacuum to yield (S)-3-amino-2-hydroxy-pentanoic acid benzylamide (380mg) as a white solid.

Step 3. (S)-3-Amino-2-hydroxy-pentanoic acid benzylamide was dissolved in a mixture of TFA/dichloromethyl (1:1; 6mL), stirred for 1 hour and evaporated to dryness. (3S)-3-Amino-2-hydroxy-pentanoic acid benzylamide was obtained as the TFA salt and used without further purification.

REFERENCE EXAMPLE 20

(S)-2-Amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol



Step 1. A mixture of 2-amino-3-hydroxy pyridine (25g, 227mmol), triethylorthoformate (75ml) and p-toluenesulfonic acid (61mg) was heated at 140°C for 8 hours. Excess triethylorthoformate was removed under vacuum. The product was crystallized from ethyl acetate to yield 22.5g of pyridyloxazole; H[1] NMR (DMSO-□): 9.26 (1H, s), 8.78 (1H, d), 8.45 (1H, d), 7.7(1H, dd); MS: 120.8 (M+1).

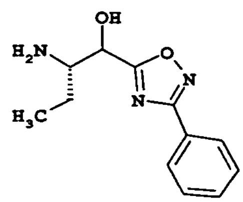
Step 2. Pyridyloxazole (600 mg, 5 mmol) in 30 ml THF was cooled to 0°C before the addition of isopropanyl magnesium chloride (2M in THF, 2.5 ml, 5 mmol). After stirring for 1 hour at 0°C, (S)-(1-formyl-propyl)-carbamic acid tert-butyl ester (573 mg, 3 mmol, Reference Example 18) in 20 ml THF was added. The ice bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was stirred for 2 hours and quenched with saturated ammonium chloride solution. Excess THF was removed and the residue was extracted with EtOAc, washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography to yield [1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-carbamic acid *tert*-butyl ester (383 mg) H[1] NMR (DMSO-□): 8.42(1H, m), 8.18(1H, m), 7.3(1H, m), 6.8, 6.6(1H, dd, d, OH, diastereomeric), 6.3, 6.02(1H, d, d, NH, diastereomeric), 4.82, 4.5(1H, m, m, diastereomeric), 1.8-1.3(2H, m), 1.2, 1.05(9H, s,s, diastereomeric), 0.89(3H, m); MS: 306.2(M-1), 308.6(M+1).

Step 3. To a stirred solution of the [1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-carbamic acid *tert*-butyl ester (12g, 100mmol) in THF (300ml) was added n-BuLi (1.6M solution in 62.5ml of hexane) drop wise under N_2 at –78°C. After 1 hour, $MgBr.Et_2O$ (25.8g, 100mmol) was added and the reaction mixture was allowed to warm to –45°C for 1 hour before being treated with 2-boc-amino-butyl-aldehyde (11.46g, 60mmol) in THF (50ml). The reaction mixture was stirred for 1 hour, quenched with saturated NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography to yield 2-boc-amino-1-(5-pyridyloxazole-2-yl)-1-butanol (14.1g).

Step 4. 2-Boc-amino-1-(5-pyridyloxazole-2-yl)-1-butanol (311mg, 1mmol) and $MeCl_2$ (5ml) were mixed and TFA (1ml) was added at room temperature. After stirring for 1 hour, the solvent and excess TFA were removed under vacuum to produce 355mg of 2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol TFA salt.

REFERENCE EXAMPLE 21

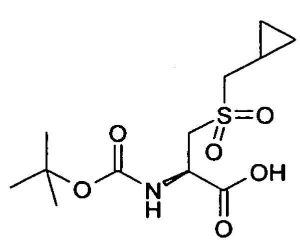
(S)-2-Amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol



3-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid (500mg, 2.14mmol) was combined with EDC (600mg, 3.14mmol), HOBt (600mg, 3.92mmol), and N-hydroxy-benzamidine (292mg, 2.14mmol). Dichloromethyl (10mL) was added and then 4-methylmorpholine (1mL). The mixture was stirred at ambient temperature for 16 hours. After dilution with ethyl acetate (200mL), the solution was washed with water (30mL), saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated under vacuum. The crude product was dissolved in pyridine (10mL) and heated at 80°C for 15 hours. The pyridine was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate) to yield 290mg (0.83mmol). The oxadiazole (145mg, 0.41mmol) was dissolved in CH_2Cl_2 (4mL) and TFA (4mL) was added. After stirring for 1 hour, the mixture was evaporated to dryness to yield (S)-2-Amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol.

REFERENCE EXAMPLE 22

(R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid



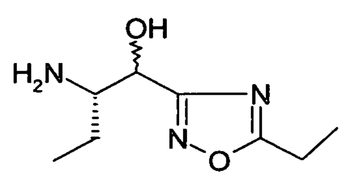
Step 1. Sodium hydroxide (2.16g, 54mmol) was dissolved in 27ml water and the solution added to a suspension of (R)-2-tert-butoxycarbonylamino-3-mercapto-propionic acid (8.2g,

37mmol) in 54ml methanol. After a clear solution had formed bromomethyl-cyclopropane (5g, 37mmol) was added and the resulting reaction mixture stirred for three days. Methanol was removed under reduced pressure. The residue was treated with 200ml 1M hydrochloric acid and then extracted three times with 200ml of dichloromethane. The combined organic phases were washed with brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 2-tert-butoxycarbonylamino-3-cyclopropylmethylsulfanyl-propionic acid (7.94g).

Step 2. Sodium hydroxide (2.32g, 58mmol) was dissolved in 75ml water. 2-tert-butoxycarbonylamino-3-cyclopropylmethylsulfanyl-propionic acid (7.94g, 29mmol) was added. A solution of Oxone™ in 100ml water was added slowly. The pH was adjusted to 3 by addition of sodium bicarbonate and the reaction mixture stirred for 30 minutes. It was extracted three times with 200ml ethyl acetate. The combined organic phases were washed with 100ml brine and dried with magnesium sulfate. The solvent was removed to yield (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (4.64g, 15mmol, 31%).

REFERENCE EXAMPLE 23

(S)-2-Amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoro-acetic acid salt



Step 1. A solution of (2-Cyano-1-ethyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (1, 9.53g, 44 mmol) in methanol (80 ml) was cooled to 0^0C and treated successively with hydroxylamine hydrochloride (3.05, 44 mmol) in methanol (80 ml) and 25% sodium methoxide solution in methanol (10.2 ml). Stirred at 0^0 C for 5 min., cold bath removed and the reaction mixture stirred at room temperature for 5hr. Methanol evaporated off under reduced pressure, crude partitioned between ethyl acetate and water. Organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure to give yellow oil. Purified by mplc eluting with a mixture of ethyl acetate – heptane to give {(S)-1-[Hydroxy-(N!-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester as white solid (3.5 g). MS: $M(H^+)$ 248.

Step 2. A mixture of {(S)-1-[Hydroxy-(N!-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (525 mg, 2.16 mmol), propionic anhydride (0.3 ml, 2.37 mmol) in dioxane (5ml) was heated at 150^0 C in a microwave (Smith Creator, S00219) for 35min. Crude evaporated under reduced pressure and purified by flash column chromatography to give {(S)-1-[(5-Ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester as yellow solid (0.8g, 67%).

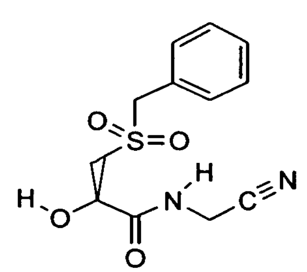
H^1 NMR ($CDCl_3$): 4.88-4.80 (2H, m), 4.01-3.84 (1H, 2 broad m), 3.64-3.45 (1H, 2 bs), 2.95-2.86 (2H, dq, J=4.2Hz, 7.6Hz), 1.73-1.62 (1H, m), 1.6-1.32 (13H, m), 1.02-0.94 (3H, q, J=7.5Hz). MS: 304(M+1)

Step 3. {(S)-1-[(5-Ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (214 mg, 0.75 mmol) in dichloromethane (3 ml)) was treated with trifluoro acetic acid at room temperature for 3h. Solvent evaporated under reduced pressure to give (S)-2-Amino-1-(5-ethyl-1,2,4-oxadiazol-3-yl)-butan-1-ol trifluoro-acetic acid salt as brown oil (0.3 g). H^1 NMR ($CDCl_3$): 7.9-7.4(3H, 2bs), 5.07 & 5.24 (1H, 2 x d, J=3.5Hz & 5.5Hz), 3.8-3.6 (1H, 2 bs), 2.96-2.87 (2H, dq, J=2.4Hz, 7.5Hz), 1.8-1.4 (2H, m), 1.40-1.34 (3H, dt, J=1.4Hz, 7.5Hz), 1.06-0.98 (3H, dt, J=7.5Hz, 10.5Hz).

MS: 186(M+1)

EXAMPLE 1

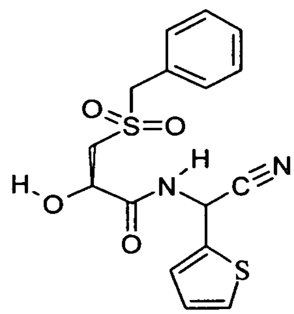
(a) <u>(*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide</u>, (Compound 4)



DMF (5mL) was added to a mixture of 2-hydroxy-3-phenylmethanesulfonyl-propionic acid [200mg, 0.82mmol, Reference Example 1(b)], EDC (300mg, 1.57mmol), HOBt (300mg, 1.96mmol) and aminoacetonitrile hydrochloride (200mg, 2.1mmol). 4-Methylmorpholine

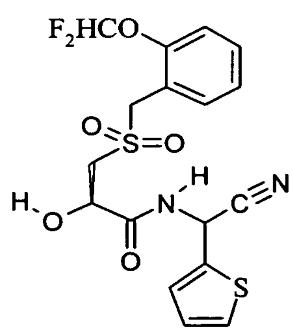
(0.5mL) was added and the mixture was stirred at ambient temperature for 2 hours. The mixture was diluted with ethyl acetate (200mL), washed with 1N HCl, brine, saturated aqueous $NaHCO_3$ solution, and brine, dried with $MgSO_4$ and evaporated under vacuum. (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide was crystallized from ethyl acetate/hexane to yield 154mg (0.55mmol); ^{1}H NMR: (DMSO) 8.89-8.77 (m, 1H), 7.46-7.37 (m, 5H), 6.71-6.62 (m, 1H), 4.60-4.45 (m, 3H), 4.17-4.08 (m, 2H), 3.39-3.28 (m, 2H). MS: (M^++1) 283.

(b) (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide, (Compound 7);



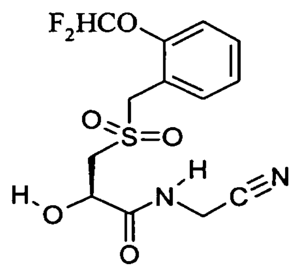
By proceeding in a manner similar to Example 1(a) above but using (R)-2-hydroxy-3-phenylmethanesulfonyl-propionic acid [Reference Example 1(b)] and DL-α-amino-2-thiopheneacetic acid there was prepared (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-2-hydroxy-3-phenylmethanesulfonyl-propionamide. ^{1}H NMR (DMSO): 9.55(d, J=6.5Hz, 1H), 7.58(d, J=5.21Hz, 1H), 7.42-7.39(m, 5H), 7.23(m, 1H), 7.05(dd, J=3.51Hz, J=5.21Hz, 1H), 6.58(dd, J=3.45Hz, J=6.66Hz, 1H), 6.41(s, 1H), 4.59-4.50(m, 3H), 3.29(s, 2H); MS: 362.6(M^{-1}), 365(M^{+1}).

(c) (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, (Compound 8)



By proceeding in a manner similar to Example 1(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid [Reference Example 1(a)] and DL-α-amino-2-thiopheneacetic acid there was prepared (*R*)-*N*-(1-cyano-1-thiophen-2-yl-methyl)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide. ^{1}HNMR (CD_3Cl): δ 7.6-7.2(m, 7H), 7.01(t, J=73.6Hz, 1H), 6.62(s, 1H), 6.21(d, J=8.15, 1H), 4.71-4.67(m, 1H), 4.46(s, 2H), 3.68(s, 2H), 3.22-3.18(m, 1H); MS: 428.6(M-1), 453(M+23).

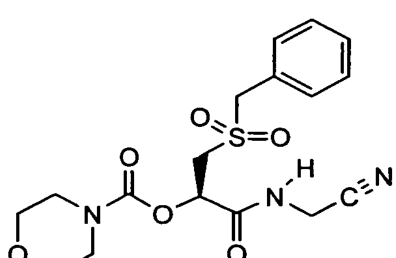
(d) (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide, (Compound 17)



By proceeding in a manner similar to Example 1(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid [Reference Example 1(a)] there was prepared (*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide. ^{1}HNMR (DMSO): 8.81(t, J=5.67Hz, 1H), 7.55-7.4(m, 2H), 7.35-7.2(m, 2H), 7.13(t, J=73.68Hz, 1H), 6.62(d, J=6.67Hz, 1H), 4.58(s, 2H), 4.52-4.45(m, 1H), 4.12(d, J=5.94Hz, 2H), 3.45-3.4(m, 2H). MS: 347.4(M-1), 371(M+23).

EXAMPLE 2

Morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester, (Compound 6);

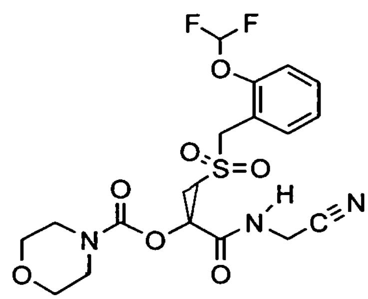


Phosgene solution (0.77mL, 1.93M in toluene) was added to CH_2Cl_2 (5mL) and cooled to 0°C under nitrogen. Quinoline (0.12mL, 1.0mmol) was added followed by (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide [100mg, 0.354mmol,

Example 1(a)]. The mixture was stirred at ambient temperature for 3 hours. Morpholine (1mmol) was added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200mL) and washed sequentially with 1N HCl, brine, saturated aqueous $NaHCO_3$ solution and brine. The product was dried with $MgSO_4$ and evaporated under vacuum and crystallized from an ethyl acetate/hexane solution to yield morpholine-4-carboxylic acid (*R*)-1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester. (85mg; 0.215mmol); ^{1}H NMR: (DMSO) 8.99-8.88 (m, 1H), 7.46-7.37 (m, 5H), 5.42-5.32 (m, 1H), 4.60-4.45 (m, 2H), 4.20-4.13 (m, 2H), 3.70-3.28 (m, 10H). MS: (M^++1) 396.

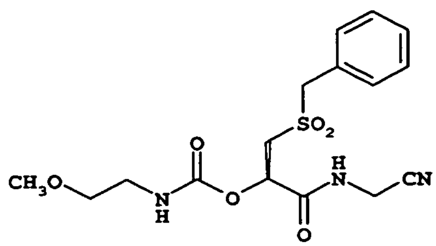
EXAMPLE 3

(a) Morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 31)



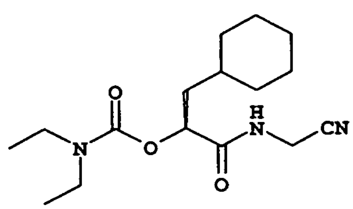
(*R*)-*N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide [100mg, 0.287mmol, Example 1(d)], was dissolved in CH_2Cl_2 (2mL). Pyridine (32.4μL, 0.4mmol) and then trichloromethylchloroformate (36.2μL, 0.3mmol) were added. The mixture was stirred at ambient temperature for 3 hours. Morpholine (0.5mL) was added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200mL), washed with 1N HCl, brine, saturated aqueous $NaHCO_3$ solution and brine. The product was dried with $MgSO_4$, evaporated under vacuum and crystallized from a solution of ethyl acetate/hexane to yield morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester (60mg; 0.130mmol); ^{1}H NMR: (DMSO) δ 8.95 (t, J=5.2Hz, 1H), 7.51-7.44 (m, 2H), 7.32-7.22 (m, 2H), 7.14 (t, $J_{H,F}$=73Hz, 1H), 5.39-5.35 (m, 1H), 4.67-4.53 (m, 2H), 4.19-4.15 (m, 2H), 3.83-3.28 (m, 10H); MS: (M^++1) 462.

(b) (R)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester



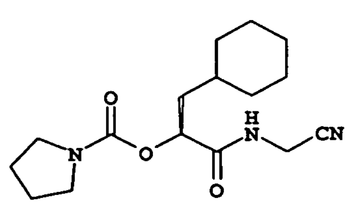
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-2-hydroxy-3-phenylmethanesulfonyl-propionamide [Example 1(a)] and 2-methoxyethylamine there was prepared <u>(R)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-phenylmethanesulfonyl-ethyl ester</u>. ^{1}H NMR: (DMSO) 8.91 (t, J=5.6Hz, 1H), 7.64 (t, J=5.6Hz, 1H), 7.40-7.32 (m, 5H), 5.30-5.25 (m, 1H), 4.59-4.50 (m, 2H), 4.17-4.13 (m, 2H), 3.58 (dd, J=9.2Hz, J=14.8Hz, 1H), 3.43 (d, 14.8Hz, 1H), 3.33 (s, 3H), 3.38-3.12 (m, 4H). MS: $(M+H)^+$ 384.

(c) <u>(S)-Diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and diethylamine there was prepared <u>(S)-Diethyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. ^{1}H NMR: (DMSO) 8.62 (t, J=5.6Hz, 1H), 4.87-4.82 (m, 1H), 4.12 (d, J=5.6, 2H), 3.42-3.10 (m, 4H), 1.72-0.82 (m, 19H). MS: $(M+H)^+$ 310.

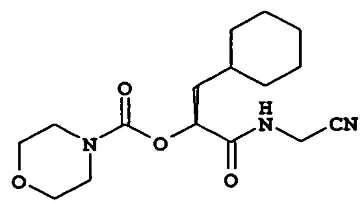
(d) <u>(S)-Pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and pyrrolidine there was prepared <u>(S)-Pyrrolidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. ^{1}H NMR: (DMSO)

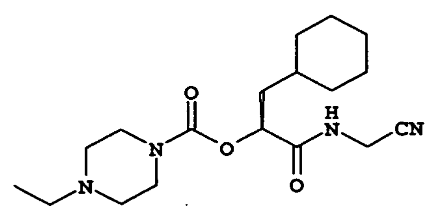
8.59 (t, J=4.8Hz, 1H), 4.86-4.81 (m, 1H), 4.11 (d, J=4.8, 2H), 3.48-3.19 (m, 4H), 1.87-0.82 (m, 17H). MS: $(M+H)^+$ 308.

(e) <u>(S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



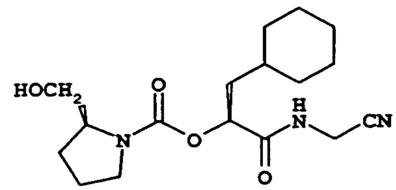
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and morpholine there was prepared <u>(S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. ^{1}H NMR: (DMSO) 8.66 (t, J=5.2Hz, 1H), 4.88-4.83 (m, 1H), 4.13 (d, J=4.8, 2H), 3.60-3.26 (m, 8H), 1.71-0.82 (m, 13H). MS: $(M+H)^+$ 324.

(f) <u>(S)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



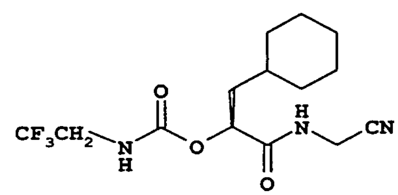
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 4-ethylpiperazine there was prepared <u>(S)-4-Ethyl-piperazine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. LC-MS: elution time = 2.08min. 349.2(M-1), 351.3(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

(g) <u>(S)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



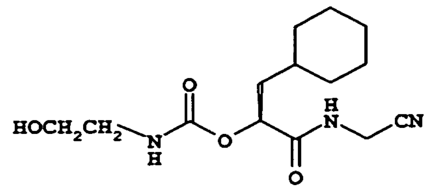
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (S)-2-hydroxymethyl-pyrrolidine there was prepared <u>(S)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. LC-MS: elution time = 3.73min. 336.5(M-1), 338.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

(h) <u>(S)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



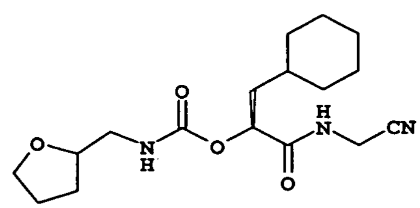
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2,2,2-trifluoroethylamine there was prepared <u>(S)-(2,2,2-Trifluoro-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>. LC-MS: elution time = 4.07min. 334.1(M-1), 336.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

(i) <u>(S)-(2-Hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester</u>



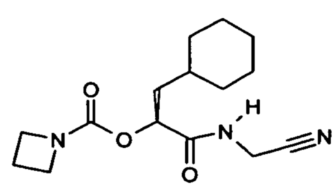
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2-hydroxyethylamine there was prepared (S)-(2-Hydroxyethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.65 (t, J=5.2Hz, 1H), 7.16 (t, J=5.2Hz, 1H), 4.85-4.80 (m, 1H), 4.62 (t, J=5.6Hz, 1H), 4.12 (d, J=5.6Hz, 2H), 3.45-3.33 (m, 2H), 3.12-2.96 (m, 2H), 1.74-0.80 (m, 13H). MS: $(M+H)^+$ 298.

(j) (Tetrahydrofuran-2-ylmethyl)-carbamic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and tetrahydrofurfurylamine there was prepared (tetrahydrofuran-2-ylmethyl)-carbamic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester as a 1:1 mixture of diastereomers, ^{1}H NMR: (DMSO) 8.66 (t, J=5.2Hz, 1H), 7.28 (t, J=5.2Hz, 1H), 4.86-4.81 (m, 1H), 4.12 (d, J=5.2Hz, 2H), 3.83-3.54 (m, 3H), 3.09-2.92 (m, 2H), 1.89-0.80 (m, 17H). MS: $(M+H)^+$ 338.

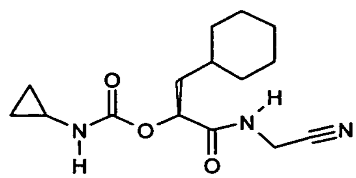
(k) (S)-Azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and azetidine there was prepared (S)-azetidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO)

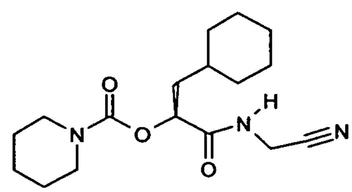
8.59 (t, J=5.2Hz, 1H), 4.82-4.77 (m, 1H), 4.11 (d, J=5.2Hz, 2H), 4.13-3.81 (m, 4H), 2.18 (quint, J=7.6Hz, 2H), 1.71-0.80 (m, 13H). MS: $(M+H)^+$ 294.

(l) (S)-Cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



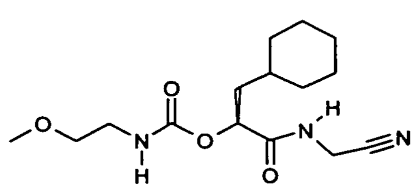
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and cyclopropylamine there was prepared (S)-cyclopropyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.64 (t, J=5.2Hz, 1H), 7.44 (br, 1H), 4.83-4.78 (m, 1H), 4.11 (d, J=5.2Hz, 2H), 2.50-2.40 (m, 1H), 1.72-0.78 (m, 13H), 0.58-0.30 (m, 4H). MS: $(M+H)^+$ 294.

(m) (S)-Piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and piperidine there was prepared (S)-piperidine-1-carboxylic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.63 (t, J=5.2Hz, 1H), 4.86-4.81 (m, 1H), 4.11 (d, J=5.6Hz, 2H), 3.48-3.20 (m, 4H), 1.70-0.82 (m, 19H). MS: $(M+H)^+$ 322.

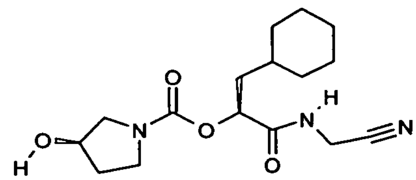
(n) (S)-(2-Methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and 2-methoxyethylamine there was prepared (S)-(2-

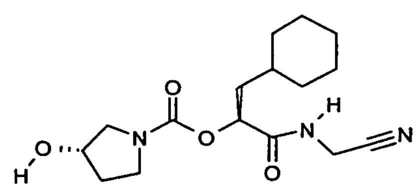
methoxy-ethyl)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.66 (t, J=5.6Hz, 1H), 7.27 (t, J=5.6Hz, 1H), 4.85-4.80 (m, 1H), 4.12 (d, J=5.6Hz, 2H), 3.40-3.03 (m, 4H), 3.32 (s, 3H), 1.74-0.80 (m, 13H). MS: $(M+H)^+$ 312.

(o) (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



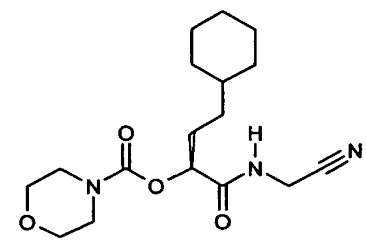
By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (R)-3-hydroxy-pyrrolidine there was prepared (R)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.64-8.56 (m, 1H), 4.98-4.80 (m, 2H), 4.29-4.20 (m, 1H), 4.11 (d, J=5.2Hz, 2H), 3.57-3.12 (m, 4H), 1.91-0.82 (m, 15H). MS: $(M+H)^+$ 324.

(p) (S)-3-Hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and (S)-3-hydroxy-pyrrolidine there was prepared (S)-3-hydroxy-pyrrolidine-1-carboxylic acid (S)-1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.63-8.55 (m, 1H), 4.98-4.90 (m, 1H), 4.85-4.80 (m, 1H), 4.28-4.19 (m, 1H), 4.13-4.09 (m, 2H), 3.54-3.09 (m, 4H), 1.93-0.81 (m, 15H). MS: $(M+H)^+$ 324.

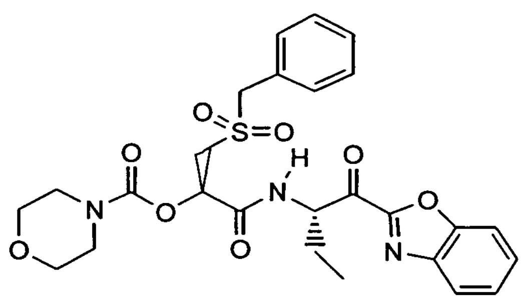
(q) (S)-Morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester



By proceeding in a manner similar to Example 3(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide and morpholine there was prepared (S)-morpholine-4-carboxylic acid 1-(cyanomethyl-carbamoyl)-3-cyclohexyl-propyl ester. ^{1}H NMR: (DMSO) 8.61 (t, J=5.6Hz, 1H), 4.79 (t, J=5.6Hz, 1H), 4.13 (d, J=5.2Hz, 2H), 3.59-3.26 (m, 8H), 1.73-1.55 (m, 7H), 1.23-1.06 (m, 6H), 0.88-0.76 (m, 2H). MS: $(M+H)^+$ 338.

EXAMPLE 4

(a) Morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 11)



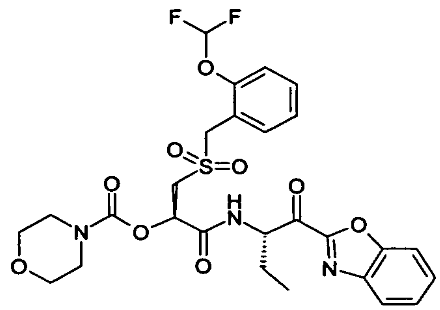
Step 1. (R)-2-Hydroxy-3-phenylmethanesulfonyl-propionic acid {2g, 8.19mmol, Reference Example 1(b)} was dissolved in CH_2Cl_2 (20mL). 4-Methylmorpholine (3.8mL) and then chloromethyl methyl ether (1.52mL, 20mmol) were added. After stirring at ambient temperature for 30 minutes, the reaction was quenched with water (50mL) and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine. The product was dried with $MgSO_4$, evaporated under vacuum and crystallized from ethyl acetate/hexane to yield 2-hydroxy-3-phenylmethanesulfonyl-propionic acid methoxymethyl ester (1.2g; 4.16mmol).

Step 2. Phosgene solution (2.07mL, 1.93M in toluene) was added to CH_2Cl_2 (10mL) and cooled to 0°C under nitrogen. Quinoline (0.95mL) was added followed by 2-hydroxy-3-phenylmethanesulfonyl-propionic acid methoxymethyl ester (250mg, 0.87mmol). The mixture was stirred at ambient temperature for 3 hours. Morpholine (0.35mL, 4mmol) was

added and stirring was continued for 3 hours. The mixture was diluted with ethyl acetate (200mL), washed sequentially with 1N HCl, brine, saturated aqueous $NaHCO_3$ solution and brine. The crude product was dried with $MgSO_4$, evaporated under vacuum and dissolved in 1,4-dioxane (20mL). 1N HCl (10mL) was added and the mixture was stirred at ambient temperature for 3 hours. Dioxane was evaporated under vacuum and the product was extracted with ethyl acetate. The combined ethyl acetate layers were washed with saturated aqueous $NaHCO_3$ solution (3x20mL). The $NaHCO_3$ solution was acidified with 6N HCl and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried with $MgSO_4$ and evaporated under vacuum to give <u>(R)-morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester.</u>

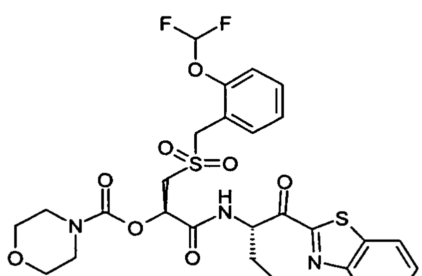
Step 3. (R)-Morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester was combined with EDC (250mg, 1.3mmol), HOBt (250mg, 1.6mmol), and (2S)-2-amino-1-benzooxazol-2-yl-butan-1-ol {250mg, 1.2mmol, Reference Example 17(a)}. Dichloromethane (4mL) was added and then 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2 hours. After dilution with ethyl acetate (150mL), the solution was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated under vacuum. The crude product was dissolved in dry dichloromethane (10mL) and Dess Martin Periodinane (500mg, 1.2mmol) was added. After stirring at ambient temperature for 1 hour, the mixture was diluted with ethyl acetate (150mL) and treated with 0.26M $Na_2S_2O_3$ solution in saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with MgSO4 and evaporated. The product was crystallized from ethyl acetate/hexane to yield <u>morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester</u> (190mg; 0.35mmol); ^{1}H NMR: (DMSO) 8.95 (d, J=6.6Hz, 1H), 8.01 (d, J=7.9Hz, 1H), 7.90 (d, J=7.9Hz, 1H), 7.65 (t, J=7.5Hz, 1H), 7.55 (t, J=7.9Hz, 1H), 7.40-7.34 (m, 5H), 5.44-5.35 (m 1H), 5.26-5.16 (m, 1H), 4.60 (d, J=13.6Hz, 1H), 4.47 (d, J=13.6Hz, 1H), 3.71-3.28 (m, 10H), 2.10-1.94 (m, 1H), 1.81-1.65 (m, 1H), 0.98 (t, J=7.2Hz, 3H); MS: $(M^{+}+1)$ 544.

(b) <u>Morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester,</u> (Compound 14)



By proceeding in a manner similar to Example 4(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid {Reference Example 1(a)} in step 1 there was prepared morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester ^{1}H NMR: (DMSO) 8.95 (d, J=6.4Hz, 1H), 8.01 (d, J=7.9Hz, 1H), 7.90 (d, J=8.4Hz, 1H), 7.65 (t, J=7.4Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.52-7.43 (m, 2H), 7.31-7.21 (m, 2H), 7.11 (t, $J_{H,F}$=73Hz, 1H), 5.43-5.37 (m 1H), 5.27-5.17 (m, 1H), 4.63 (d, J=13.5Hz, 1H), 4.54 (d, J=13.5Hz, 1H), 3.88-3.28 (m, 10H), 2.10-1.94 (m, 1H), 1.81-1.65 (m, 1H), 0.98 (t, J=7.6Hz, 3H); MS: (M^++1) 610.

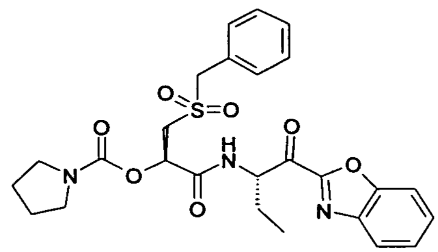
(c) morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 15).



By proceeding in a manner similar to Example 4(a) above but using (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid {Reference Example 1(a)} in step 1 and (2S)-2-amino-1-benzothiazol-2-yl-butan-1-ol {Reference Example 17(b)} in step 3 there was prepared morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester. ^{1}H NMR: (DMSO) 8.93 (d, J=6.4Hz, 1H), 8.30-8.24 (m, 2H), 7.72-7.62 (m, 2H), 7.51-7.44 (m, 2H), 7.32-7.22 (m, 2H), 7.12 (t, $J_{H,F}$=73Hz, 1H), 5.49-5.35 (m 2H), 4.64 (d, J=13.5Hz, 1H), 4.55 (d, J=13.5Hz, 1H), 3.91-3.28 (m, 10H), 2.08-1.94 (m, 1H), 1.84-1.68 (m,

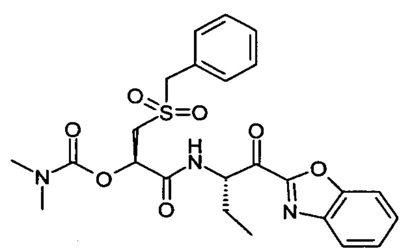
1H), 0.99 (t, J=7.6Hz, 3H). MS: (M^{+}+1) 626.

(d) Pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 19).



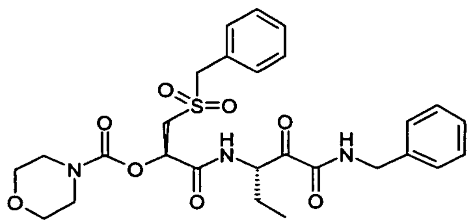
By proceeding in a manner similar to Example 4(a) above but using pyrrolidine in step 2 there was prepared pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester. ^{1}H NMR: (DMSO) 8.90 (d, J=6.4Hz, 1H), 7.99 (d, J=7.9Hz, 1H), 7.89 (d, J=8.4Hz, 1H), 7.65 (t, J=7.4Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.40-7.33 (m, 5H), 5.41-5.33 (m 1H), 5.26-5.15 (m, 1H), 4.59 (d, J=13.5Hz, 1H), 4.47 (d, J=13.5Hz, 1H), 3.66-3.17 (m, 6H), 2.10-1.64 (m, 6H), 0.97 (t, J=7.2Hz, 3H); MS: (M^{+}+1) 528.

(e) Dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 20).



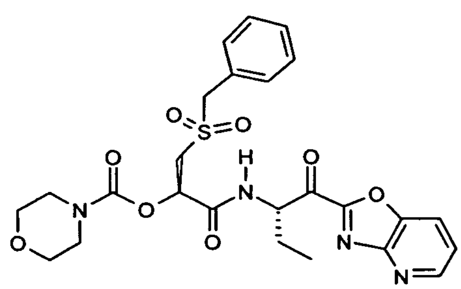
By proceeding in a manner similar to Example 4(a) above but using dimethylamine in step 2 there was prepared dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester. ^{1}H NMR: (DMSO) 8.91 (d, J=6.4Hz, 1H), 7.99 (d, J=7.9Hz, 1H), 7.90 (d, J=8.4Hz, 1H), 7.65 (t, J=7.4Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.40-7.33 (m, 5H), 5.39-5.33 (m 1H), 5.26-5.15 (m, 1H), 4.59 (d, J=13.5Hz, 1H), 4.47 (d, J=13.5Hz, 1H), 3.63 (dd, J=14.8Hz, J=10.6Hz, 1H), 3.42 (dd, J=14.8Hz, J=2.5Hz, 1H), 2.89 (s, 3H), 2.79 (s, 3H), 2.10-1.94 (m, 1H), 1.81-1.64 (m, 1H), 0.97 (t, J=7.2Hz, 3H); MS: (M^{+}+1) 502.

(f) Morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 25).



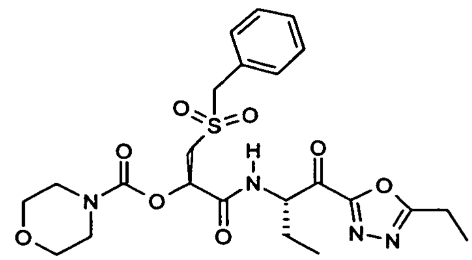
By proceeding in a manner similar to Example 4(a) above but using (R)-3-amino-2-hydroxy-pentanoic acid benzylamide TFA salt (Reference Example 19) in step 3 there was prepared morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester. ^{1}H NMR: (DMSO) 9.27 (t, J=5.5Hz, 1H), 8.67 (d, J=8.1Hz, 1H), 7.40-7.20 (m, 10H), 5.42-5.34 (m 1H), 4.96-4.85 (m, 1H), 4.64-4.24 (m, 4H), 3.66-3.28 (m, 10H), 1.90-1.72 (m, 1H), 1.63-1.46 (m, 1H), 0.89 (t, J=7.2Hz, 3H); MS: (M^++1) 560.

(g) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester



By proceeding in a manner similar to Example 4(a) above but using (S)-2-amino-1-oxazolo[4,5-b]pyridin-2-yl-butan-1-ol TFA salt (Reference Example 20) there was prepared morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester. ^{1}H NMR: (DMSO) 9.00 (d, J=6.4Hz, 1H), 8.73 (m, 1H), 8.39 (d, J=8.4Hz, 1H), 7.69-7.64 (m, 1H), 7.45-7.30 (m, 5H), 5.37 (d, J=10.4Hz, 1H), 5.19-5.13 (m, 1H), 4.57 (d, J=13.6Hz, 1H), 4.46 (d, J=13.6Hz, 1H), 3.67-3.23 (m, 10H), 2.10-1.98 (m, 1H), 1.80-1.69 (m, 1H), 0.99 (t, J=7.0Hz, 3H). MS: $(M+H)^+$ 545.

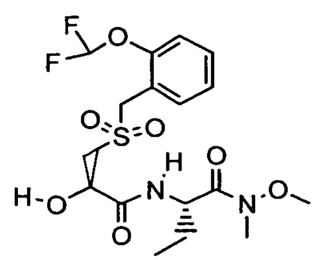
(h) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester



By proceeding in a manner similar to Example 4(a) above but using 2-amino-1-(5-ethyl-[1,3,4]oxadiazol-2-yl-butan-1-ol {Reference Example 11(m)}there was prepared morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester. ^{1}H NMR: (DMSO) 8.95 (d, J=6.0Hz, 1H), 7.41-7.33 (m, 5H), 5.35 (d, J=10.0Hz, 1H), 4.97-4.91 (m, 1H), 4.63-4.45 (m, 2H), 3.64-3.23 (m, 10H), 2.96 (q, J=7.2Hz, 2H), 1.99-1.89 (m, 1H), 1.75-1.64 (m, 1H), 1.30 (t, J=7.6Hz, 3H), 0.94 (t, J=7.2Hz, 3H). MS: $(M+H)^+$ 523.

EXAMPLE 5

(S)-2-{(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino}-*N*-methoxy-*N*-methyl-butyramide, (Compound 32)

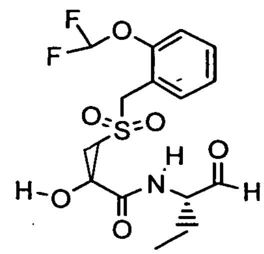


To a solution of (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionic acid {1.24g, 4mmol, Reference Example 1(a)} in CH_2Cl_2 (20ml) was added HOBt (0.74g, 4.8mmol), EDC (1.15g, 6mmol), (R)-2-amino-*N*-methoxy-*N*-methyl-butyramide TFA salt (1.04g, 4mmol), prepared as in reference 2, and NMM (1.6g, 16mmol). After stirring for 14 hours at room temperature, the reaction mixture was diluted with 150ml of ethyl acetate. The mixture was washed with saturated $NaHCO_3$ and brine before drying with anhydrous $MgSO_4$. This crude product was then filtered, concentrated and purified by flash column chromatography using silica gel with hexane/ acetate as eluent to yield (S)-2-{(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino}-*N*-methoxy-*N*-methyl-butyramide (1.45g); 1HNMR (CD3Cl): 7.6-7.5(d, J=7.67Hz, 1H), 7.5-7.35(m, 2H), 7.31-7.15(m, 2H), 6.63(t, J=73.4Hz, 1H), 5.0-4.85(br., 1H), 4.7-4.6(m, 1H), 4.55-4.48(m, 2H),

4.45-4.35(m, 1H), 3.80(s, 3H), 3.6-3.8(m, 1H), 3.35-3.2(m, 1H), 1.78(s, 3H), 2.0-1.5(m, 2H), 0.93(t, J=6.9Hz, 3H); MS: 437.4.4(M-1), 439.4(M+1).

EXAMPLE 6

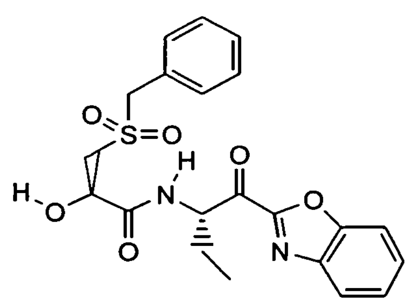
(R)-3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-*N*-((S)-1-formyl-propyl)-2-hydroxy-propionamide. (Compound 23)



To a solution of (S)-2-{(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propanoylamino}-*N*-methoxy-*N*-methyl-butyramide (1.3g, 3mmol, Example 5) in ethyl ether (50mL) at 0°C under N_2, was added 1N LAH solution of ethyl ether (3ml). After stirring for 3 hours at 0°C, 1ml of ethyl acetate and saturated NH_4Cl solution was added. The crude product was then extracted with ether, washed with brine, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography using silica gel with hexane/ acetate as eluent to yield (R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-*N*-((S)-1-formyl-propyl)-2-hydroxy-propionamide (0.66g); ^{1}HNMR (DMSO): 9.43(s, 1H), 8.42(d, J=7.45Hz, 1H), 7.6-7.0(m, 4H), 7.12(t, J=73.93Hz, 1H), 6.52(d, J=6.45Hz, 1H), 5.2-5.17(m, 1H), 4.65-4.53(m, 2H), 4.12-4.0(m, 1H), 3.63-3.55(m, 2H), 1.7-1.4(m, 2H), 0.89(t, J=6.8Hz, 3H); MS: 378.2(M-1), 380.4(M+1).

EXAMPLE 7

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide, (Compound 5)

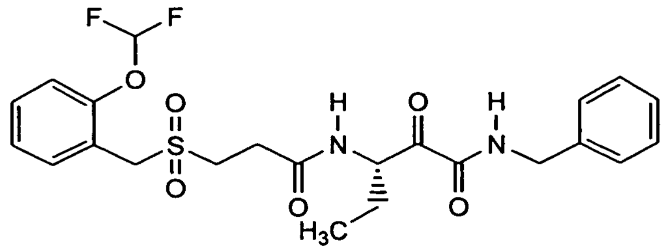


Step 1. To a solution of (R)-3-Phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionic acid {556mg, 1mmol, Reference Example 3} in CH_2Cl_2 (10mL) at room temperature was added HOBt (183mg, 1.2mmol), EDC (288mg, 15mmol), (S)-2-Amino-1-benzooxazol-2-yl-butanol (206mg, 1mml) and NMM (202mg, 2mmol). The mixture was then stirred overnight at room temperature before being diluted with ethyl acetate (100mL), washed with saturated $NaHCO_3$, brine, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified by flash column chromatography using silica gel with hexane/acetate as eluent (to yield 180mgs of product). This compound was dissolved in CH_2Cl_2, Dess-Martin Periodinane (196mg, 0.46mmol) was added at room temperature and the mixture was stirred for 2 hours. Saturated $Na_2S_2O_3$-$NaHCO_3$ solution (5mL) was added and stirred for a further 30 minute before extraction with ethyl acetate and washing sequentially with saturated $NaHCO_3$ solution and brine. The crude product was then dried with anhydrous $MgSO_4$, filtered, concentrated and purified by flash column chromatography using silica gel with hexane/acetate as eluent to yield (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionamide.

Step 2. (R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionamide (120mg, 0.2mmol), in CH_3CN (10mL), 48% HF/ water solution (1mL) were mixed and stirred at room temperature for 16 hours. Saturated $NaHCO_3$ solution was added carefully to adjust the pH to between 8 and 9. The product was extracted with ethyl acetate (100mL), washed with brine and dried with magnesium sulfate. The solvent was removed and the product crystallized from acetate and hexane to yield <u>(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide</u> as a white solid (85% yield); ^{1}H NMR: (DMSO) 8.29 (d, J=7.9Hz,1H), 7.74 (d, J=7.9Hz, 1H), 7.59 (t, J=8.1Hz, 1H), 7.46-7.35 (m, 7H), 6.52 (d, J=6.6Hz, 1H), 5.08-4.99 (m, 1H), 4.58-4.47 (m, 3H), 3.35-3.28 (m, 2H), 2.05-1.90 (m, 1H), 1.81-1.65 (m, 1H), 0.91 (t, J=7.2Hz, 3H); MS: (M^++1) 431.

<u>EXAMPLE 8</u>

(a) <u>(S)-3-{3-[2-(1,1-Difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide</u>, (Compound 27)



Step 1. A mixture of (R)-3-amino-2-hydroxy-pentanoic acid benzylamide TFA salt (70mg, 0.22mmol), 3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionic acid (64mg, 0.22mmol, Reference Example 19) HOBT (33mg,0.22mmol), EDC (63mg, 0.325mmol), 1mL dichloromethane and N-methyl morpholine (48μL, 0.434mmol). The mixture was allowed to stir 16 hours. The product was extracted into 60mL ethyl acetate and washed with two 10mL portions of 1N HCl, 10mL water, and two 10mL portions of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give 105mg of crude (R)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-hydroxy-pentanoic acid benzylamide (0.21mmol, 100% yield).

Step 2. To a 1mL dichloromethane solution of 105 mg of (R)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-hydroxy-pentanoic acid benzylamide (0.21 mmol) was added Dess Martin periodinane (179mg, 0.42 mmol). The mixture was allowed to stir for 16 hours, then 10mL of 0.26M $Na_2S_2O_3$ in saturated $NaHCO_3$ was added and the mixture was extracted with two 30mL portions of ethyl acetate and washed with three 15mL portions of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The product was purified by silica gel chromatography using 3:1 hexane:ethyl acetate eluent and crystallized from diethyl ether and hexane to give (S)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide (28mg, 0.054mmol, 26% yield); ^{1}H NMR: ($CDCl_3$) 7.0-7.47 (m, 9H), 6.49 (m, 1H), 6.24 (m, 1H), 5.22 (m, 1H), 4.40 (m, 2H), 4.30 (m, 3H), 3.23 (m, 2H), 2.70 (m, 2H), 2.01 (m, 1H), 1.68 (m, 1H), 0.85 (m, 3H); MS: (M^++1) 499.4, 496.53.

The following compounds were prepared by the method of Example 8: *N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propionamide (Compound 26); ^{1}H NMR: ($CDCl_3$) 7.85 (d, J=7.6Hz, 1H), 7.7-7.0 (m, 7H), 6.51 (m, 2H), 5.60 (m, 1H), 4.34 (m, 3H), 3.29 (m, 2H), 2.80 (m, 2H), 2.13 (m, 1H), 1.87 (m, 1H), 0.96 (m, 3H); MS: (M^++1) 481, 480.48;

N-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-3-*p*-tolylmethanesulfonyl-propionamide (Compound 30); [1]H NMR: ($CDCl_3$) 7.9 (m, 1H), 7.62 (m, 1H), 7.56 (td,J=6.9,1.2Hz, 1H), 7.47 (td,J=7.1,1.2Hz, 1H), 7.3-7.1 (m, 9H), 6.47 (d,J=7.7Hz, 1H), 5.71 (m, 1H), 4.22 (s, 2H), 3.20 (m, 2H), 2.71 (m, 4H), 2.47 (m, 1H), 2.33 (s, 3H), 2.21 (m, 1H); MS: (M^{+}+1) 505.2, 504.60.

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-pyrrolidin-1-yl-propyl)-propionamide;

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-3-morpholin-4-yl-2,3-dioxo-propyl)-propionamide;

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-(1-ethyl-2,3-dioxo-3-piperazin-1-yl-propyl)-propionamide;

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-[3-(1,1-dioxo-116-thiomorpholin-4-yl)-1-ethyl-2,3-dioxo-propyl]-propionamide;

3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-[1-ethyl-3-(4-methyl-sulfonyl-piperazin-1-yl)-2,3-dioxo-propyl]-propionamide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid dimethylamide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid cyclopentyl-ethyl-amide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid phenylamide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid pyridin-3-ylamide;

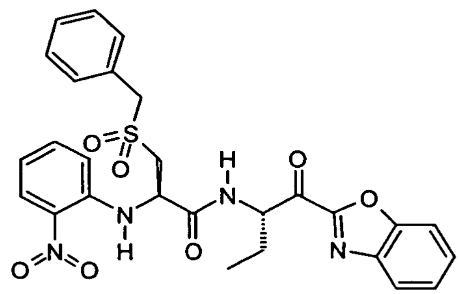
3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (tetrahydro-pyran-4-yl)-amide;

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (1-benzoyl-piperidin-4-yl)-amide; and

3-[3-(2-Difluoromethoxy-phenylmethanesulfonyl)-propionylamino]-2-oxo-pentanoic acid (2-morpholin-4-yl-ethyl)-amide.

EXAMPLE 9

(R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 28)



Step 1. 3-Benzylsulfanyl-2-(2-nitro-phenylamino)-propionic acid (350mg, 1.05 mmol, Reference Example 5) was dissolved in 20mL methanol, treated with a 20mL aqueous solution of Oxone® (970mg, 0.12mmol), and stirred for 72 hours. Water (300mL) was added and the precipitate was filtered and dried to give 2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionic acid (215mg, 0.59mmol, 56%yield)

Step 2. A mixture of 2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionic acid (215mg, 0.59mmol), HOBT (136mg, 0.148mmol), EDC (408mg, 2.13mmol), (S)-2-amino-1-benzooxazol-2-yl-butan-1-ol (122mg, 0.59mmol, {Reference Example 17(a)}, 2.4mL dichloromethane and N-methyl morpholine (97□L, 0.89mmol) was allowed to stir 16 hours. The product was extracted into 20mL ethyl acetate and washed with three 5mL portions of 1N HCl, and one 30mL portion of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethane-sulfonyl-propionamide (223mg, 0.40mmol, 45% yield).

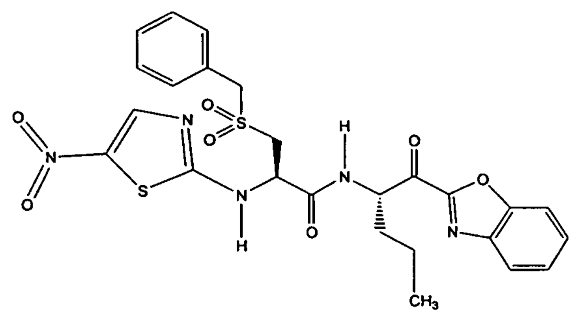
Step 3. (R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethane-sulfonyl-propionamide (223mg, 0.4mmol) was dissolved in 1.6mL dichloromethane and treated with Dess Martin periodinane (342mg, 0.80 mmol). The mixture was allowed to stir for 16 hours, then 20mL of 0.26M $Na_2S_2O_3$ in saturated $NaHCO_3$ was added and the mixture was extracted with two 30mL portions of ethyl acetate and washed with three 5mL portions of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was dissolved in a minimum amount of hot ethyl acetate and crystallized by addition of dry diethyl ether. This crystallization was repeated to give clean <u>(R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide</u> (97mg, 0.176mmol, 44% yield); ^{1}H NMR: (DMSO) 8.67 (m, 1H), 8.12 (m, 1H), 7.81 (m, 1H), 7.65-7.35 (m, 10H), 6.78 (m, 2H), 5.51 (m, 1H),

4.68 (m, 1H), 4.37 (s, 2H), 3.62 (m, 1H), 3.38 (m, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 0.98 (m, 3H); MS: (M^{+}+1) 551.0, 550.58.

The following compound was prepared by the method of Example 9: N-[1-(Benzooxazole-2-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(pyrimidin-2-ylamino)-propionamide.

EXAMPLE 10

(R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 29)



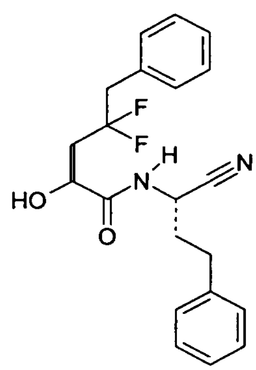
Step 1. A mixture of (R)-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionic acid (42mgmg, 0.123mmol, Reference Example 6) HOBT (28mg, 0.148mmol), EDC (29mg, 0.148mmol), (S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol {27mg, 0.123mmol, Reference Example 17(c)}, 1mL dichloromethane and N-methyl morpholine (14□L, 0.123mmol) was allowed to stir for 16 hours. The product was extracted into 60mL ethyl acetate and washed with one 30mL portion of 1N HCl, and one 30mL portion of saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionamide (41.8mg, 0.077mmol, 63% yield).

Step 2. (R)-*N*-[(S)-1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-butyl]-3-benzylsulfanyl-2-(5-nitro-thiazol-2-ylamino)-propionamide (41.8mg, 0.077mmol) was dissolved in 0.5mL methanol, treated with a 0.5mL aqueous solution of Oxone® (43mg, 0.069mmol), and stirred for 1 hour. Methanol was removed under reduced pressure and 2mL water was added. The mixture was extracted with two 10mL portions of ethyl acetate, dried over $MgSO_4$, and concentrated. It was then dissolved in 0.5mL dichloromethane and treated with Dess Martin periodinane (65mg, 0.154 mmol). The mixture was allowed to stir for 16 hours, then 5mL of

0.26M $Na_2S_2O_3$ in saturated $NaHCO_3$ was added and the mixture was extracted with two 10mL portions of ethyl acetate and washed with three 5mL portions of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The product was purified by triturating with diethyl ether to give (R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide (28mg, 054mmol, 26% yield); ^{1}H NMR: ($CDCl_3$) 7.96 (s, 1H), 7.87 (m, 1H), 7.7-7.3 (m, 9H), 5.57 (m, 1H), 5.06 (m, 1H), 4.47 (m, 2H), 3.75 (m, 1H), 3.48 (m, 1H), 2.09 (m, 1H), 1.85 (m, 1H), 1.43 (m, 1H), 1.24 (m, 1H), 0.94 (m, 3H); MS: (M^++1) 572.2, 571.63.

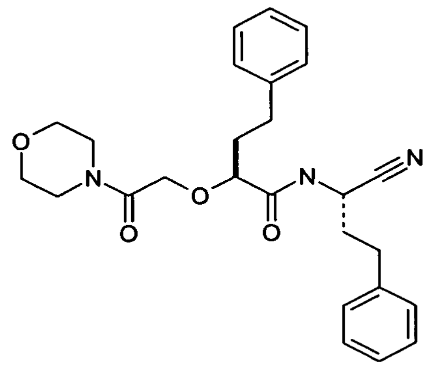
EXAMPLE 11

(a) (2S) (4,4-Difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide, (Compound 33)



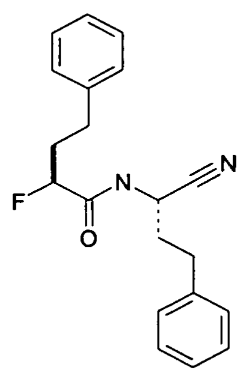
To a mixture of amino-acetonitrile hydrochloride (0.37 mmol, 72.6mg), (2S)-4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1.0 eq., 0.37 mmol, 85.0mg, Reference Example 7) and N,N-diispropylethylamine (2.2 eq., 0.81 mmol, 105.2mg) in dry dichloromethane (4 mL) under nitrogen was added PyBOP® (1.1 eq., 0.41 mmol, 212mg). The mixture was stirred at room temperature for 15.5 hours and then concentrated in vacuum. The residue was diluted with ethyl acetate (30ml) and the mixture was washed with water (30mL), then with sodium bicarbonate (30mL) and then with water (30mL). The organic layer was dried over MgSO4 and then concentrated in vacuum. The residue was purified over 10g silica gel, eluting with a mixture of ethyl acetate and heptane (1:2, v/v) to afford (2S) (4,4-difluoro-2-hydroxy-5-phenyl-pentanoic acid (1(S)-cyano-3-phenyl-propyl)-amide as a light tan solid (67.4 mg, 48.9%). ^{1}H NMR ($CDCl_3$) 7.3 (m, 10H), 7.1 (d, J=7 Hz, 1H), 4.8 (q, J=7.4 Hz, 1H), 4.53 (bd, J=9.5 Hz, 1H), 3.2 (dt, J=16.2, 4.2 Hz, 2H), 2.96 (s, 1H), 2.85 (m, 2H), 2.5 (m, 1H), 2.3-0.9 (m, 3H). LC/MS 89% parent (M+1).

(b) N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide, (Compound 34)



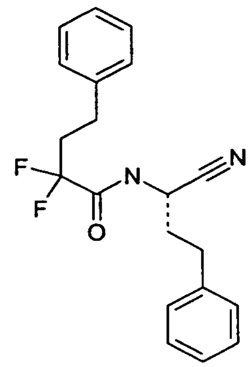
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyric acid [Reference Example 8] there was prepared N-(1(S)-cyano-3-phenyl-propyl)-2-(S)-(2-morpholin-4-yl-2-oxo-ethoxy)-4-phenyl-butyramide as an oil. ^{1}H NMR ($CDCl_3$) 9.4 (d, J=8.2 Hz, 1H), 7.3 (m, 10H), 4.75 (q, J=7.5 Hz, 1H), 4.63 (d, J=15.1 Hz, 1H), 3.95 (d, J=15.3 Hz, 1H), 3.87 (dd, J=8.2, 3.9 Hz, 1H), 3.7 (m, 6H), 3.32 (m, 2H), 2.85 (m, 4H), 2.1 (m, 3H), 2.05 (m, 1H). LC/MS 100% (M+1) 450.

(c) N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide, (Compound 35)



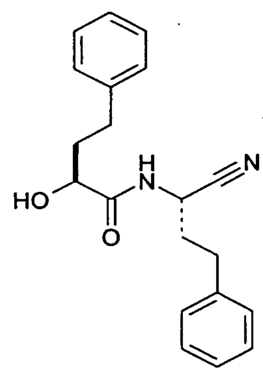
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2S)-2-fluoro-4-phenyl-butyric acid (Reference Example 9) there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-fluoro-4-phenyl-butyramide as a light tan solid. ^{1}H NMR ($CDCl_3$) 7.3 (m, 10H), 6.6 (bs, 1H), 4.95 (ddd, J=49.2, 8.2, 3.5 Hz, 1H), 4.8 (m, 1H), 3.8 (m, 4H), 2.3 (m, 1H), 2.2 (m, 3H). MS (CI, M+1) 325.

(d) N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide, (Compound 36)



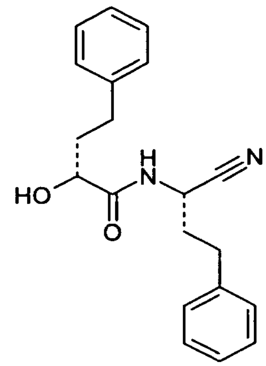
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 2,2-difluoro-4-phenyl-butyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2,2-difluoro-4-phenyl-butyramide as a white solid. ^{1}H NMR ($CDCl_3$) 7.3 (m, 10H), 6.6 (d, J=8.1 Hz, 1H), 4.83 (q, J=7.4 Hz, 1H), 2.88 (dt, J=7.5, 2.5 Hz, 2H), 2.79 (t, J=8 Hz, 2H), 2.4 (m, 2H), 2.2 (q, J=7.5 Hz, 2H). LC/MS 50% (M+1) 343.

(e) N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide, (Compound 37)



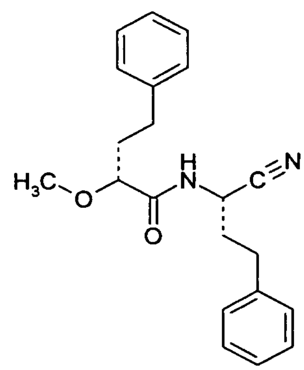
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2S)-2-hydroxy-4-phenyl-butyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2-(S)-hydroxy-4-phenyl-butyramide as a white solid. ^{1}H NMR ($CDCl_3$) 7.3 (m, 10H), 6.9 (d, J=8.4 Hz, 1H), 4.86 (q, J=7.4 Hz, 1H), 4.2 (m, 1H), 2.84 (t, J=7.1 Hz, 2H), 2.77 (t, J=7.8 Hz, 2H), 2.5 (d, J=4.7 Hz, H), 2.2 (m, 3H), 1.95 (m, 1H). LC/MS 49% (M+1) 323.

(f) N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide, (Compound 38)



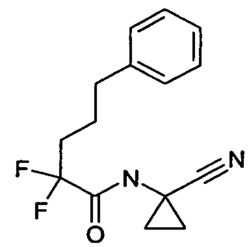
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and (2R)-2-hydroxy-4-phenyl-butyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-hydroxy-4-phenyl-butyramide as a white solid. ^{1}H NMR ($CDCl_3$) 7.4-7.1 (m, 10H), 6.9 (d, J=8.7 Hz, 1H), 4.87 (q, J=7.3 Hz, 1H), 4.1 (m, 1H), 2.85 (t, J=7.5 Hz, 2H), 2.77 (t, J=8.4 Hz, 2H), 2.3 (d, J=5.1 Hz, 1H), 2.2 (m, 3H), 2.0 (m, 1H). LC/MS 94% (M+1) 323.

(g) N-(1-(S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide, (Compound 39)



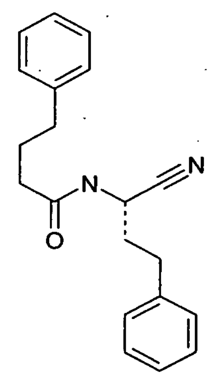
By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride (0.407 mmol, 80mg) and 2(R)-methoxy-4-phenyl-butyric acid (Reference Example 10) there was prepared N-(1-S)-cyano-3-phenyl-propyl)-2-(R)-methoxy-4-phenyl-butyramide as a white solid (91.8mg, 67%). ^{1}H NMR ($CDCl_3$) 7.2 (m, 10H), 6.8 (d, J=8.5 Hz, 1H), 4.86 (q, J=7.5 Hz, 1H), 3.67 (dd, J=6.5, 4.5 Hz, 1H), 3.35 (s, 3H), 2.85 (m, 2H), 2.68 (t, J=8.0 Hz, 2H), 2.2-2.0 (m, 4H). LC/MS 84% (M^+1) 337.

(h) 2,2-Difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide, (Compound 40)



By proceeding in a manner similar to Example 11(a) above but using 2,2-difluoro-5-phenyl-pentanoic acid and 1-amino-cyclopropanecarbonitrile hydrochloride there was prepared 2,2-difluoro-5-phenyl-pentanoic acid (1-cyano-cyclopropyl)-amide. ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 2H), 1.64 (m, 2H), 1.82 (m, 2H), 2.12 (m, 2H), 2.8-2.56 (m, 2H), 6.82 (m, 1H), 7.36-7.15 (m, 5H). MS (ES-) 277.

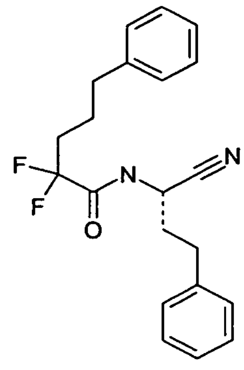
(i) N-(1-(S)-Cyano-3-phenyl-propyl)-4-phenyl-butyramide, (Compound 41)



By proceeding in a manner similar to Example 11(a) above but using (S)-2-amino-4-phenyl-butyronitrile hydrochloride and 4-phenylbutyric acid there was prepared N-(1-(S)-cyano-3-phenyl-propyl)-4-phenyl-butyramide as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 10H), 6.0 (d, J=8.3 Hz, 1H), 4.9 (q, J=7.4 Hz, 1H), 2.8 (m, 2H), 2.65 (t, J=7.4 Hz, 2H), 2.15 (m, 4H), 1.95 (m, 2H). LC/MS 100% (M+1) 307.

EXAMPLE 12

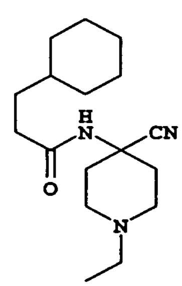
2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide, (Compound 42)



A mixture of 2,2-difluoro-5-phenyl-pentanoic acid (109mg, 0.509 mmol), (S)-2-amino-4-phenyl-butyronitrile hydrochloride (103mg, 0.523 mmol) and HATU (206mg, 0.542 mmol) in DMF (4mL) and stirred at room temperature for 5hours then evaporated under reduced pressure. The residue was taken in ethyl acetate washed with 1N HCl, sodium bicarbonate and then water. Organic extract was dried over Na_2SO_4 and then evaporated under vacuum to give orange oil. The residue was subjected to mplc, eluting with a mixture of ethyl acetate and heptane (1:9, v/v) to give 2,2-difluoro-5-phenyl-pentanoic acid ((S)-1-cyano-3-phenyl-propyl)-amide as colorless oil (82 mg). ^{1}H NMR ($CDCl_3$) 7.3-7.1 (m, 10H), 6.9 (bs, 1H), 4.80 (q, J=7.5 Hz, 1H), 2.80 (dt, J=7.3, 2.7 Hz, 2H), 2.65 (t, J=7.5 Hz, 2H), 2.2-2.0 (m, 4H), 1.8 (m, 2H). MS 357 (MH^+), 379 (M+Na).

EXAMPLE 13

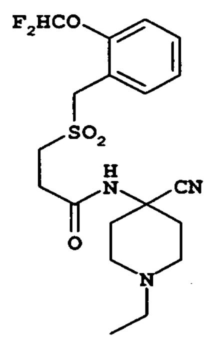
(a) *N*-(4-Cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide



Step 1. To a stirred solution of 1-ethyl-4-piperidone(25g, 0.197mol) in 300ml of diethyl ether, and NH_4Cl(22.3g, 0.41mol), was added NaCN(14.5g, 0.295mol, in 70ml water) drop-wise at room temperature. After stirring for 24h the diethyl ether was separated and the water phase was extracted with n-BuOH, then washed with brine and dried. After removal of most of the n-BuOH under reduced pressure, the residue was diluted with 50ml of diethyl ether and then acidified with 2N HCl in diethyl ether solution at 0°C. The solid was dried under vacuum to yield 45g of 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt.

Step 2. To a stirred mixture of 3-cyclohexyl-propionic acid (156mg, 1mmol), 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt (227, 1mmol, prepared as in step 1 above), and HATU (570mg, 1.5mmol) in $MeCl_2$ (5ml), was added N,N-diisopropylethylamine (516mg, 4mmol) at room temperature. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield *N*-(4-Cyano-1-ethyl-piperidin-4-yl)-3-cyclohexyl-propionamide (170mg). LC-MS: elution time = 2.25min. 290.2(M-1), 292.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

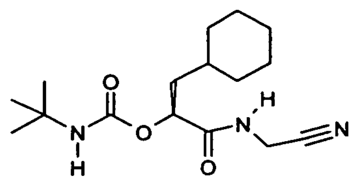
(b) *N*-(4-Cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide



By proceeding in a similar manner to Example 13(a) but using 3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionic acid (294mg, 1mmol) and 4-amino-1-ethyl-piperidine-4-carbonitrile HCl salt(227, 1mmol) there was *N*-(4-cyano-1-ethyl-piperidin-4-yl)-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide 260mg). LC-MS: R_T =1.96min., 428.2(M-1), 430.3(M+1). MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

EXAMPLE 14

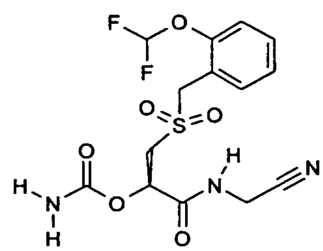
(S)-tert-Butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



(S)-N-Cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide (53mg, 0.252mmol) was dissolved in dichloromethane (1mL). Triethylamine (0.1mL) was added and then tert.-butyl isocyanate (0.034mL, 0.3mmol). The mixture was stirred at room temperature overnight. After dilution with ethyl acetate (100mL), the solution was washed with 1N aqueous. HCl, brine, sat. aqueous $NaHCO_3$, and brine, dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate 1:1) gave (S)-tert-Butyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester (63mg, 0.204mmol) as a white solid.

EXAMPLE 15

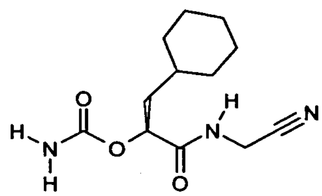
(a) (R)-Carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester



(R)-N-Cyanomethyl-3-(2-(1,1-difluoromethoxy)-phenylmethanesulfonyl)-2-hydroxy-propionamide {100mg, 0.287mmol, Example 1(a)} was dissolved in dichloromethane (2mL) and THF (1mL). Trichloroacetyl isocyanate (0.051mL, 0.43mmol) was added and the mixture was stirred for 1h. The solvents were removed under vacuum and the residue was dissolved in 1,4-dioxane (10mL). 1N aqueous. HCl (5mL) was added and the mixture was heated at 70°C for 4h. After cooling to room temperature, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography on silica gel (hexane/ ethyl acetate 1:3) gave (R)-carbamic acid 1-(cyanomethyl-carbamoyl)-2-(2-difluoromethoxy-phenylmethanesulfonyl)-ethyl ester

(35mg, 0.089mmol) as a white solid. ^{1}H NMR: (DMSO) 8.90 (t, J=4.8Hz, 1H), 7.48-7.43 (m, 2H), 7.30-7.21 (m, 2H), 7.11 (t, $J_{H,F}$=73.6Hz, 1H), 6.98-6.76 (br, 2H), 5.28-5.23 (m, 1H), 4.60 (s, 2H), 4.15 (d, J=4.8Hz, 2H), 3.70 (dd, J=10.0Hz, J=14.8Hz, 1H), 3.54 (d, J=14.4Hz, 1H). MS: $(M+H)^{+}$ 392.

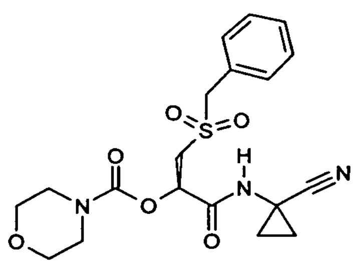
(b) (S)-Carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester



By proceeding in a manner similar to Example 8(a) above but using (*R*)-*N*-cyanomethyl-3-cyclohexyl-2-hydroxy-propionamide there was prepared (S)-Carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclohexyl-ethyl ester. ^{1}H NMR: (DMSO) 8.63 (t, J=5.6Hz, 1H), 6.63 (br, 2H), 4.81-4.77 (m, 1H), 4.11 (d, J=5.2Hz, 2H), 1.74-0.81 (m, 13H). MS: $(M+H)^{+}$ 254.

EXAMPLE 16

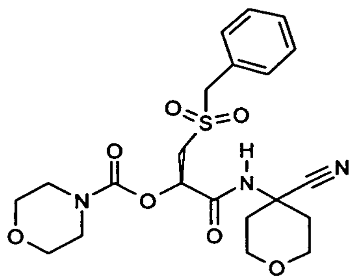
(a) (R)-Morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester



DMF was added to a mixture of (R)-morpholine-4-carboxylic acid 1-carboxy-2-phenylmethanesulfonyl-ethyl ester {from step 2 in Example 4(a)} (60mg, 0.168mmol), HATU (200mg, 0.52mmol), and 1-amino-cyclopropanecarbonitrile hydrochloride (100mg, 0.84mmol). 4-Methylmorpholine (0.5mL) was added and the mixture was stirred overnight. The mixture was diluted with ethyl acetate (100mL), washed with 1N aqueous. HCl, brine, sat. aqueous. $NaHCO_3$, brine, dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography on silica gel (hexane/ethyl acetate 1:2) gave (R)-morpholine-4-carboxylic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester (7mg, 0.017mmol). ^{1}H NMR: (DMSO) 9.16 (s, 1H), 7.40-7.32 (m, 5H), 5.24-5.19 (m, 1H), 4.55 (d,

J=13.2Hz, 1H), 4.48 (d, J=13.2Hz, 1H), 3.63-3.25 (m, 10H), 1.51-1.39 (m, 2H), 1.20-1.07 (m, 2H). MS: $(M+H)^+$ 422.

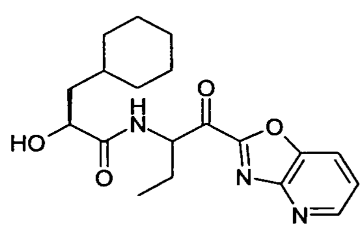
(b) (R)-Morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester



By proceeding in a manner similar to Example 16(a) above but using 4-amino-tetrahydropyran-4-carbonitrile hydrochloride {prepared according to Example 13(a) step1 but using tetrahydropyran-4-one} there was prepared (R)-morpholine-4-carboxylic acid 1-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-2-phenylmethanesulfonyl-ethyl ester. LC-MS: elution time = 3.20min. 464.4(M-1), 466.2(M+1). (MS: API 150EX. LC: HP Agilent 1100 Series. Column: Phenomenex, 5u ODS3 100A 100X3mm.; Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

EXAMPLE 17

3-Cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide



Step 1. To a stirred solution of [1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-carbamic acid *tert*-butyl ester (3.11g, 10mmol, prepared as described in Reference Example 20 step2.) in dioxane (4ml) was added HCl (4N solution in 5ml of dioxane) at room temperature. After 2 hours, ethyl ether(50ml) was added and the reaction mixture was filtered. The resultant solid was washed with an additional 20ml of ethyl ether and dried under vacuum to yield 3g of 2-amino-1-oxazolo[4,5-*b*]pyridin-2-yl-butan-1-ol HCl salt.

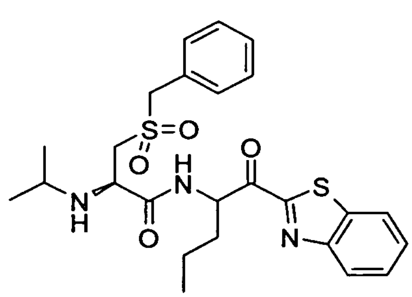
Step 2. To a stirred mixture of 3-cyclohexyl-2-hydroxy-propionic acid (155mg, 0.9mmol), 2-amino-1-oxazolo[4,5-*b*]pyridin-2-yl-butan-1-ol HCl salt, and HOBt (168mg, 1.1mmol) in MeCN (5ml), was added EDC (270mg, 1.4mmol) and N-methylmorpholine (0.45ml) at 23°C. After stirring for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, dried with $MgSO_4$ and concentrated to yield 293 mg of <u>3-cyclohexyl-2-hydroxy-*N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-propionamide</u>.which was used in step 3 following without further purification. MS: 360.3(M-1), 362.3(M+1), 384.2(M+Na).

Step 3. To a stirred solution of 3-cyclohexyl-2-hydroxy-*N*-[1-(hydroxy-oxazolo[4,5-*b*]pyridin-2-yl-methyl)-propyl]-propionamide (300mg, 0.83mmol) in $MeCl_2$(20ml), was added MnO_2(1.44g, 16.6mmol) at room temperature. After stirring for 30min. the mixture was filtered to remove MnO_2, and washed with 20ml of $MeCl_2$. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography to yield <u>3-cyclohexyl-2-hydroxy-*N*-[1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide</u> (40mg). H^1 NMR (DMSO-□): 8.71(1H, dd, NH, diastereomer), 8.38(1H, dd,), 8.28(1H, m), 7.7-7.6(1H, m), 5.5-5.4(1H, m), 5.2-5.1(1H, m), 3.95-3.991H, br., OH), 2.1-1.95(1H, m), 1.85-1.75(1, m), 1.7-0.8(16H, m).

MS: 358.1 (M-1), 360.1 (M+1), 382(M+Na).

<u>EXAMPLE 18</u>

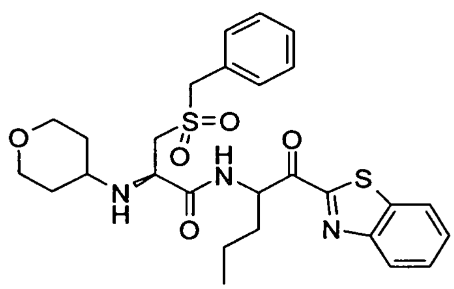
(a) <u>(R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide</u>



A solution of (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide {30mg, 0.06mmol, Example 30(a)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (51mg, 0.12mmol). This mixture was

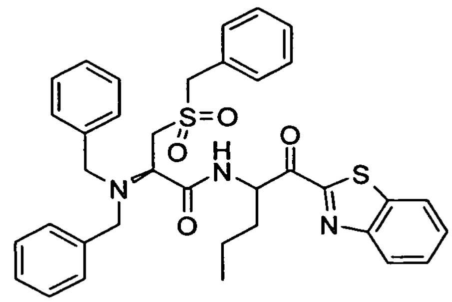
stirred at room temperature for 45 minutes then treated with resin-bound thiosulfate (400mg, 0.6mmol) and stirring was continued for a further 24 hours then the mixture was treated with AP-Trisamine (270mg, 0.6mmol). After stirring for a further 24 hours the reaction mixture was filtered and the filtrate was evaporated to give (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (23mg, 75%) as mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300MHz): 8.29-8.27 (m, 1H), 8.23-8.19 (m, 1H), 8.01-7.98 (m, 1H), 7.63-7.36 (m, 7H), 5.80-5.74 (m, 1H), 4.36-4.31 (m, 2H),[3.79 (dd, J=9.5Hz,3Hz), 3.73 (dd, J=9Hz, 2.5Hz) 1H], 3.41-3.34 (m, 1H), 3.20-3.01 (m, 1H), 2.89-2.85 (m, 1H), 2.17-2.06 (m, 1H), 1.88-1.78 (m, 1H), 1.52-1.25 (m, 3H), 1.12-1.06 (m, 6H), [0.96 (t, J=7.5Hz) 0.95 (t, J=7.5Hz) 1H]. LC/MS m/z=502 (M+H).

(b) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



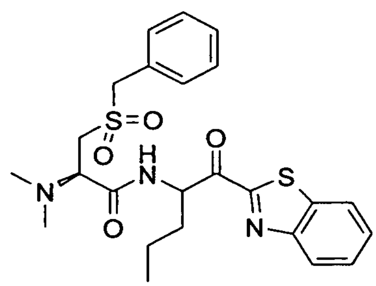
By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.11 mmol, Example 29(b)} and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (10mg, 16%). LC/MS retention time 2.92min (TIC), m/z=544 (M+H) (determined with method A).

(c) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide {0.11 mmol, Example 29(a)} and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide (4mg) as mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300MHz): 8.33-7.89 (m, 3H), 7.61-7.55 (m, 2H), 7.47-7.29 (m, 15H), 5.75 (m, 1H), [4.54 (d, J=14Hz), 4.51 (d, J=13.5Hz), 1H], [4.27 (d, J=14Hz), 4.25 (d, J=13.5Hz), 1H], 4.11-3.95 (m, 2H), [3.78 (d, J=13Hz), 3.76 (d, J=13Hz), 2H], [3.51 (d, J=13Hz), 3.50 (d, J=13Hz), 2H], 3.19-3.13 (m, 1H), 2.10-1.77 (m, 2H), 1.51-1.37 (m, 2H), 0.91-084 (m, 3H). LC/MS m/z=640 (M+H).

(d) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide

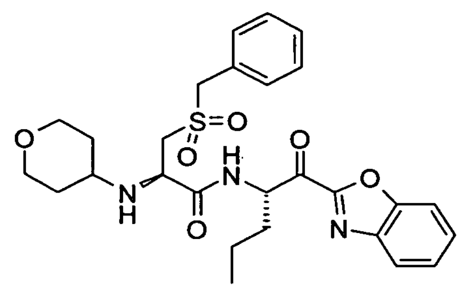


By proceeding in a similar manner to Example 18(a) but using (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide {30mg, 0.06mmol, Example 30(b)}, and subjecting the crude product to HPLC there was prepared (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (11mg, 38%).

LC/MS retention time 2.98min (TIC), m/z=488 (M+H) (determined with method A).

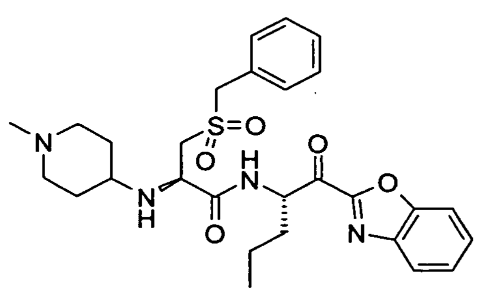
EXAMPLE 19

(a) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



A solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.22mmol, Example 31(a)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (187mg, 0.44mmol). This mixture was agitated at room temperature overnight then treated with resin-bound thiosulfate (1.47g, 2.2mmol) and stirring was continued for a further 24 hours then the mixture was treated with Silicycle Triamine (611mg, 2.2mmol). After agitating for a further 24 hours the reaction mixture was filtered. The filtrate was evaporated and the residue was subjected to HPLC to give (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (9mg, 8%). LC/MS retention time 3.0min (TIC), m/z=528 (M+H) (determined with method B).

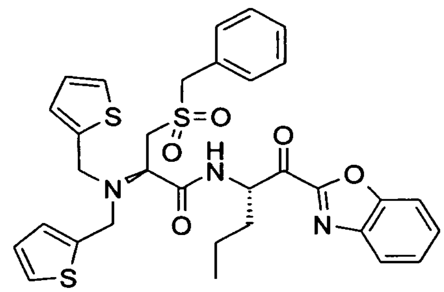
(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide {0.22mmol, Example 31(b)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide (7mg, 6%).

LC/MS retention time 2.7min (TIC), m/z=541 (M+H) (determined with method A).

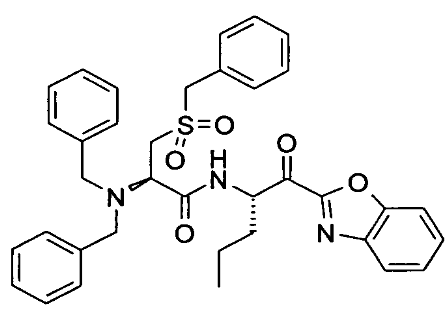
(c) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide {0.22mmol, Example 31(c)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide (5.3mg, 4%)

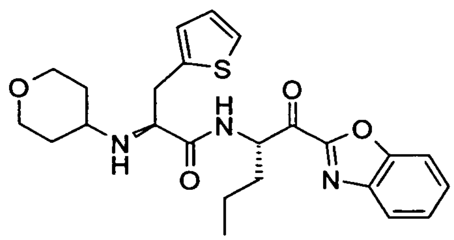
LC/MS retention time 3.7min (TIC), m/z=636 (M+H) (determined with method A).

(d) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide



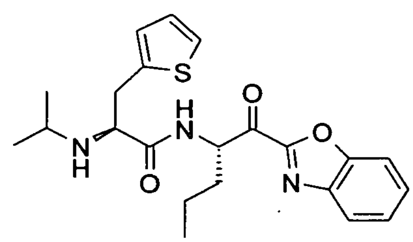
By proceeding in a similar manner to Example 19(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide {0.22mmol, Example 31(d)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide (3.8mg, 3%). LC/MS retention time 4.14min (TIC), m/z=624 (M+H) (determined with method B).

(e) (S)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide



By proceeding in a similar manner to Example 19(a) but using (S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide {0.22mmol, Example 31(e)} there was prepared (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide (6.5mg, 6%). LC/MS retention time 2.92min (TIC), m/z=456 (M+H) (determined with method B).

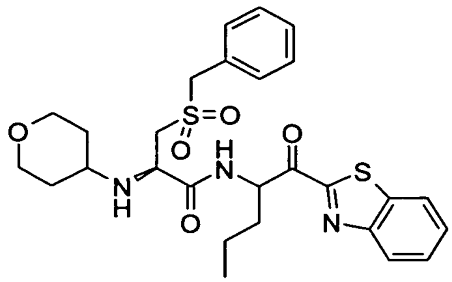
(f) (S)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide



By proceeding in a similar manner to Example 19(a) but using (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide {0.22mmol, Example 31(f)}, there was prepared (S)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide (10.6mg,12%). LC/MS retention time 2.99min (TIC), m/z=414 (M+H) (determined with method B).

EXAMPLE 20

(a) (R)-N-[1-(Benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



A solution of (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.22mmol, Example 32(a)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (187mg (0.44mmol). After stirring at room temperature for 30minutes the reaction mixture was treated with saturated sodium thiosulfate solution (50ml) and saturated sodium bicarbonate solution (50ml). The phases were separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash chromatography using a silica gel cartridge to give (R)-N-[1-(benzothiazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (46mg, 38%) as mixture of diastereoisomers. The two diastereomers were separated by silica gel column chromatography eluting with 1:1 v/v heptane- ethyl acetate mixture.

Diastereoisomer A:

^{1}H NMR ($CDCl_3$, 300MHz): 8.23-8.20 (m, 2H), 8.00 (dd, J=7Hz, 2Hz, 1H), 7.63-7.53 (m, 2H), 7.48-7.40 (m, 5H), 5.80 (m, 1H), 4.38 (d, J=14Hz, 1H), 4.32 (d, J=14Hz, 1H), 3.97-3.90 (m, 2H), 3.80 (dd, J=9.5Hz, 3Hz, 1H), 3.43-3.30 (m, 3H), 3.13 (dd, J=14.5Hz, 9.5Hz, 1H), 2.70 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 1.91-1.76 (m, 3H), 1.52-1.37 (m, 4H), 0.95 (t, J=7.5Hz, 3H).

LC/MS m/z=544 (M+H)

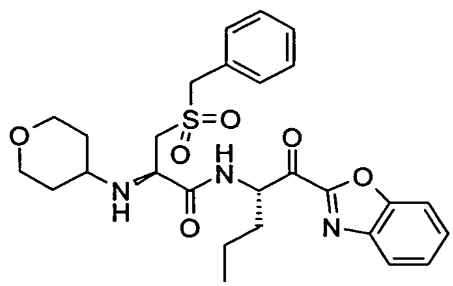
Diastereoisomer B:

^{1}H NMR ($CDCl_3$, 300MHz): 8.22-8.19 (m, 2H), 8.01-7.98 (m, 1H), 7.63-7.53 (m, 2H), 7.44-7.37 (m, 5H), 5.74 (m, 1H), 4.35-4.31 (m, 2H), 3.99-3.94 (m, 2H), 3.86 (dd J=9.5Hz, 3Hz, 1H), 3.49-3.33 (m, 3H), 3.08 (dd, J=14.5Hz, 9.5Hz), 2.75-2.70 (m, 1H), 2.22 (m, 1H), 2.15-2.06 (m, 1H), 1.91-1.75 (m, 3H), 1.53-1.37 (m, 4H), 0.96 (t, J=7.5Hz, 3H).

LC/MS m/z=544 (M+H)

(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-

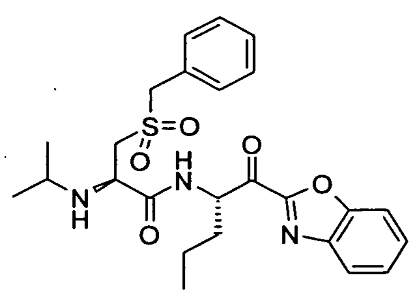
(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 20(a) but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {0.22mmol, Example 32(b)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (48mg, 41%). ^{1}H NMR ($CDCl_3$, 300MHz): 8.22 (d, J=8.5Hz, 1H), 7.92 (d, J=8Hz, 1H), 7.68 (d, J=8.5Hz, 1H), 7.60-7.40 (m, 7H), 5.68-5.61 (m, 1H), 4.37 (d, J=14HZ, 1H), 4.31 (d, J=14Hz, 1H), 3.97-3.91 (m, 2H), 3.80 (dd, J=9.5Hz, 3Hz, 1H), 3.43-3.32 (m, 3H), 3.12 (dd, J=14.5Hz, 9.5Hz, 1H), 2.73-2.66 (m, 1H), 2.26 (m, 1H), 2.13-2.05 (m, 1H), 1.89-1.77 (m, 3H), 1.52-1.39 (m, 4H), 0.97 (t, J=7.5Hz, 3H). LC/MS m/z=528 (M+H).

EXAMPLE 21

(a) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide

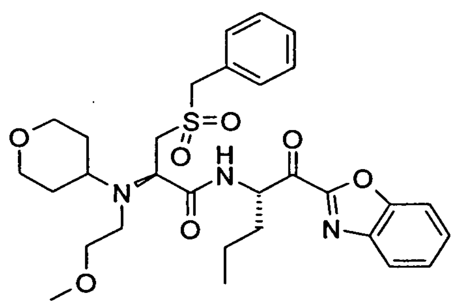


A solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide {30mg, 0.063mmol, Example 31(g)} in dichloromethane (10mL) was treated with Dess-Martin-periodinane (53mg, 0.126mmol) and this mixture was stirred at room temperature for 1 hour then subjected to The Mettler-Toledo Allex™ liquid handler work-up as described below:

Dichloromethane (15ml) was added to the reaction mixture, followed by a 1:1 mixture (8ml) of saturated sodium thiosulfate solution and saturated sodium bicarbonate solution. The

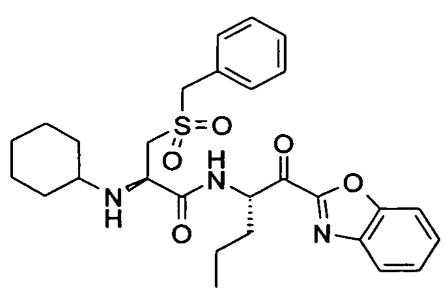
phases were separated and the organic phase washed with another 5ml of the thiosulfate/bicarbonate solution. The organic phase was then washed with brine and then dried over magnesium sulfate. The crude product was subjected to flash chromatography using a silica gel cartridge to give (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl propionamide (6.2mg, 20%). LC/MS retention time 2.7min (TIC), m/z=486 (M+H) (determined with method C).

(b) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide {80mg, 0.136 mmol, Example 32(d)} there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide (7mg, 9%). LC/MS retention time 3.5min (TIC), m/z=586 (M+H) (determined with method C).

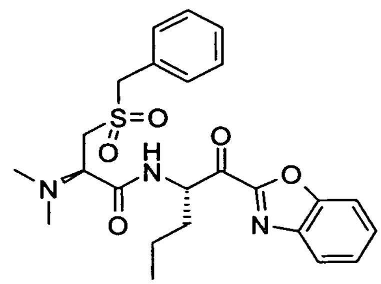
(c) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide

{48mg, 0.091mmol, Example 32(e)} there was prepared (R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide (7.9mg, 16%). LC/MS retention time 2.99-3.02min (TIC), m/z=526 (M+H) (determined with method C).

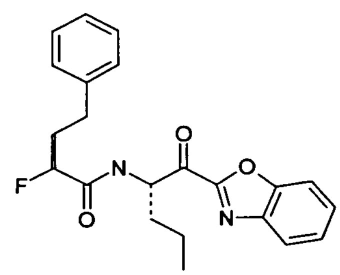
(d) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a similar manner to Example 21(a) but using (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide {10mg, 0.021mmol, Example 32(f)} there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (2.5mg, 24%). LC/MS retention time 2.82min (TIC), m/z=472 (M+H) (determined with method C).

EXAMPLE 22

(1S)-N-[1-(Benzooxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide



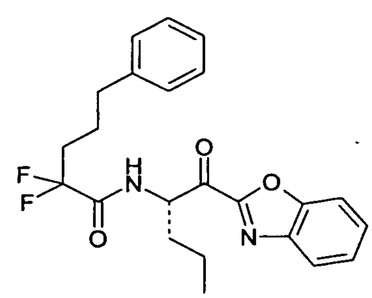
Step 1. To a mixture of (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {0.549 mmol, 121 mg, Reference Example 17(c)}, (S)-2-fluoro-4-phenyl-butyric acid (1.0 eq., 0.549 mmol, 100 mg, Reference Example 9) and N,N-diisopropylethylamine (1.1 eq., 0.604 mmol, 78 mg) in dry dichloromethane (5 mL) under nitrogen was added PyBOP® (1.1 eq., 0.603 mmol, 285 mg). The mixture was stirred at room temperature for 23.5 hr, then concentrated in vacuum. The residue was diluted with ethyl acetate (20 mL) and washed with sodium bicarbonate (30 mL) then water (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuum. The

residue was purified by silica gel column chromatography, eluting with ethyl acetate and heptane (1:2) to afford (S)-N- [(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-fluoro-4-phenyl-butyramide as mixture of diastereoisomers (167.8 mg, 79.5%).

Step 2. To a solution of (S)-N- [(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-fluoro-4-phenyl-butyramide in dry dichloromethane (5mL) under nitrogen was added a 15% (wt in dichloromethane, 2.0 eq, 0.863 mmol, 2.44 g) of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane). The mixture was stirred at room temperature for 2 hr, then quenched by adding a solution of $Na_2S_2O_3$ (4.0 eq., 1.73 mmol, 273 mg) in saturated Sodium bicarbonate solution (30 ml). The organic layer was dried (MgSO4) and concentrated in vacuum. The residue was purified over 10 g silica gel, eluting with ethyl acetate and heptane (1:3) to afford (1S)-N-[1-(Benzooxazole-2-carbonyl)-butyl]-2-(S)-fluoro-4-phenyl-butyramide as a light yellow solid (156 mg, 94%). ^{1}H NMR ($CDCl_3$) 7.95 (d, J=7.9 Hz, 1H), 7.7 (d, J=8.2 Hz, 1H), 7.6 (t, J=7.3 Hz, 1H), 7.51 (t, J=7.4 Hz, 1H), 7.2 (m, 6H), 5.8 (m, 1H), 4.95 (ddd, J=49.4, 8, 3.5 Hz, 1H), 2.8 (m, 2H), 2.4 (m, 1H), 2.2 (m, 2H), 1.85 (m, 1H), 1.5 (m, 2H), 1.0 (t, J=7.3 Hz, 3H). LC/MS 86% (M+1) 383.

EXAMPLE 23

2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide



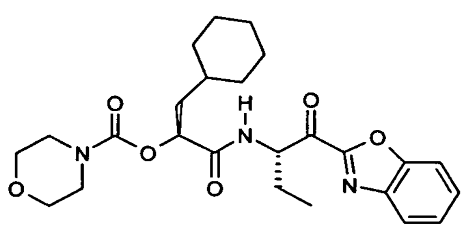
Step 1. A solution 2,2-Difluoro-5-phenyl-pentanoic acid (182 mg, 0.85 mmol) in DMF (10 mL) was treated with (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol (187 mg, 0.85 mmol), HATU (323 mg, 0.85 mmol) and N,N-Diisopropylethylamine (0.162 mL) and stirred at room temperature for 5 ½ hrs. DMF evaporate off, crude taken up in ethyl acetate and washed with 1N HCl, saturated $NaHCO_3$ and brine. Dried over Na_2SO_4 and evaporated under reduced pressure to give an oil. Purification by column chromatography eluting with 1:1 mixture of

ethyl acetate and heptane gave 2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-amide as orange oil (216 mg).
MS 417 (MH^+).

Step 2. A solution of 2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-amide (216 mg, 0.52 mmol) in dichloromethane (10 mL) was treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (220 mg, 0.52 mmol) for 1hr at room temperature. The reaction mixture was washed with 0.5 M $Na_2S_2O_3$, saturated $NaHCO_3$, and water and dried over Na_2SO_4. Solvent evaporated under reduced pressure and crude purified by flash chromatography eluting with mixture of ethyl acetate and heptane to give <u>2,2-Difluoro-5-phenyl-pentanoic acid [(S)-1-(benzoxazole-2-carbonyl)-butyl]-amide</u> as off white solid (90 mg).
^1H NMR ($CDCl_3$) 7.93 (d, J=8 Hz, 1H), 7.68 (d, J=8 Hz, 1H), 7.59 (t, J=8 Hz, 1H), 7.49 (t, J=8 Hz, 1H), 7.3-7.11 (m, 5H), 5.72 (m, 1H), 2.67 (t, J=7.5 Hz, 2H), 2.22-2.07 (m, 3H), 1.92-1.77 (m, 3H), 1.55-1.26 (m, 2H), 0.96 (t, J=7.4Hz, 3H).
LC/MS 415(M+1).

EXAMPLE 24

(a) <u>Morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester</u>



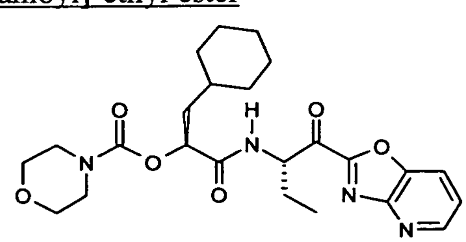
Step 1. (S)-3-Cyclohexyl-2-hydroxy-propionic acid (3g, 17.4mmol) was dissolved in methanol (30mL). Trimethylorthoformate (5mL) and p-toluenesulfonic acid monohydrate (100mg) was added. The mixture was stirred at ambient temperature overnight. Water (50mL) was added and stirring was continued for 2h. Methanol was removed under vacuum and the aqueous residue was extracted with ethyl acetate (3x50mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated. (S)-3-Cyclohexyl-2-hydroxy-propionic acid methyl ester was obtained as a colorless liquid (3.1g; 16.7mmol).

Step 2. (S)-3-Cyclohexyl-2-hydroxy-propionic acid methyl ester (1g, 5.37mmol) was dissolved in dichloromethane (20mL). Pyridine (0.57mL, 7mmol) was added and the solution was cooled to 0°C under nitrogen. Trichloromethylchloroformate (0.66mL, 5.5mmol) was added and the mixture was stirred for 30min at room temperature. Morpholine (0.5mL) was added and stirring was continued for 2h. After dilution with ethyl acetate (200mL), the solution was washed with 1N aqueous. HCl and brine, dried with $MgSO_4$ and evaporated under vacuum. The residue was dissolved in methanol (50mL) and 1N aqueous. NaOH solution (20mL) was added. The mixture was stirred at room temperature for 4h. Methanol was removed under vacuum and the aqueous residue was washed with diethylether. The aqueous layer was acidified with 1N aqueous HCl and extracted with ethyl acetate (3x100mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and evaporated under vacuum. The crude (S)-morpholine-4-carboxylic acid 1-carboxy-2-cyclohexyl-ethyl ester was used without further purification.

Step 3. By proceeding in a similar manner to that described in step3 Example 4(a) but using (S)-morpholine-4-carboxylic acid 1-carboxy-2-cyclohexyl-ethyl ester there was prepared <u>morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-2-cyclohexyl-ethyl ester</u>.
^{1}H NMR: (DMSO) 8.61 (d, J=6.4Hz, 1H), 7.97 (d, J=8.0Hz, 1H), 7.87 (d, J=8.0Hz, 1H), 7.61 (t, J=8.0Hz, 1H), 7.52 (t, J=8.0Hz, 1H), 5.15-5.09 (m, 1H), 4.91-4.86 (m, 1H), 3.56-3.20 (m, 8H), 2.05-1.93 (m, 1H), 1.79-0.78 (m, 14H), 0.96 (t, J=7.2Hz, 3H). MS: $(M+H)^+$ 472.

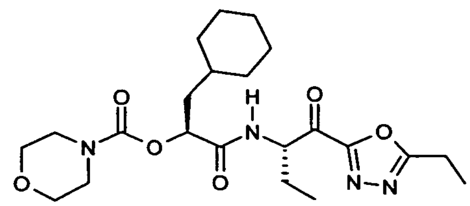
By proceeding in a similar manner to Example 24(a) there was prepared:

(b) <u>Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester</u>



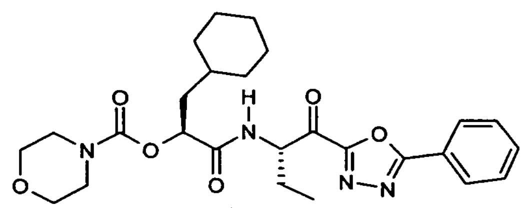
^{1}H NMR: (DMSO) 8.73-8.69 (m, 2H), 8.38 (d, J=8.0Hz, 1H), 7.67-7.62 (m, 1H), 5.08-5.02 (m, 1H), 4.88-4.83 (m, 1H), 3.57-3.20 (m, 8H), 2.07-1.95 (m, 1H), 1.79-0.75 (m, 14H), 0.97 (t, J=7.2Hz, 3H). MS: $(M+H)^+$ 473;

(c) Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester



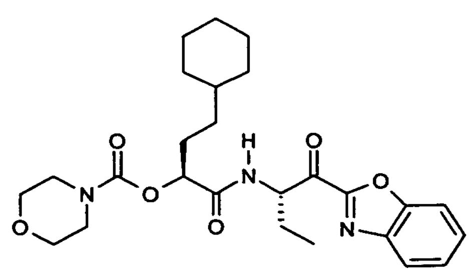
^{1}H NMR: (DMSO) 8.62 (d, J=4.8Hz, 1H), 4.94-4.84 (m, 2H), 3.57-3.20 (m, 8H), 2.95 (q, J=7.2Hz, 2H), 1.98-1.87 (m, 1H), 1.74-0.82 (m, 14H), 1.29 (t, J=7.2Hz, 3H), 0.93 (t, J=7.2Hz, 3H). MS: $(M+H)^+$ 451;

(d) Morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-ethyl ester



^{1}H NMR: (DMSO) 8.69 (d, J=6.0Hz, 1H), 8.07 (d, J=8Hz, 2H), 7.70-7.59 (m, 3H), 4.99-4.92 (m, 1H), 4.88-4.83 (m, 1H), 3.57-3.20 (m, 8H), 2.03-1.92 (m, 1H), 1.77-0.77 (m, 14H), 0.96 (t, J=7.2Hz, 3H). MS: $(M+H)^+$ 499;

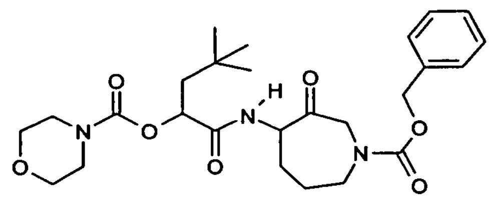
(e) Morpholine-4-carboxylic acid (S)-1-[(S)-1-(benzooxazole-2-carbonyl)-propylcarbamoyl]-3-cyclohexyl-propyl ester



^{1}H NMR: (DMSO) 8.60 (d, J=6.8Hz, 1H), 7.97 (d, J=8.0Hz, 1H), 7.87 (d, J=8.0Hz, 1H), 7.61 (t, J=8.0Hz, 1H), 7.52 (t, J=8.0Hz, 1H), 5.13-5.06 (m, 1H), 4.81-4.76 (m, 1H), 3.56-3.21 (m, 8H), 2.05-1.93 (m, 1H), 1.79-1.46 (m, 8H), 1.19-0.90 (m, 6H), 0.96 (t, J=7.2Hz, 3H), 0.77-0.62 (m, 2H). MS: $(M+H)^+$ 486;

EXAMPLE 25

4-[4,4-Dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl ester



Sodium hydride (60% in mineral oil, 10g, 250mmol) was suspended in dry DMF. Allyl-carbamic acid benzyl ester (19.1g, 100mmol) was added dropwise at ambient temperature. After stirring for 5min, 5-bromo-1-pentene (25g, 168mmol) was added dropwise. Stirring was continued at 50°C for 1h. The reaction was quenched with water and then partitioned between diethylether and water. The ether layer was washed with water and brine, dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography (ethyl acetate/hexane 1:9) gave 15.5g allyl-pent-4-enyl-carbamic acid benzyl ester.

Allyl-pent-4-enyl-carbamic acid benzyl ester (15.5g, 59.8mmol) was dissolved in dichloromethane and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (1g) was added. The mixture was refluxed under a nitrogen atmosphere until TLC analysis showed complete reaction. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (ethyl acetate/hexane 1:9). Yield: 7.8g 2,3,4,7-Tetrahydro-azepine-1-carboxylic acid benzyl ester.

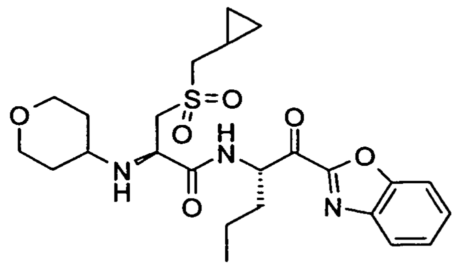
To a solution of 2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (4.5g, 19.45mmol) in dichloromethane (50mL) was added m-chloroperbenzoic acid (60mmol). The mixture was stirred at ambient temperature for 16h. Sat aqueous K_2CO_3 solution was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with sat. aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated under vacuum. The crude epoxide was dissolved in a 8:1 methanol/water mixture (100mL). Ammonium chloride (3.2g,

60mmol) and sodium azide (3.9g, 60mmol) was added and the mixture was heated at 60°C for 48h. Most of the solvent was removed under vacuum. The residue was extracted with ethyl acetate. The combined organic layers were washed with sat. aqueous $NaHCO_3$ (200mL) and brine (200mL), dried with $MgSO_4$ and evaporated under vacuum. Flash chromatography of the residue (hexane/ethyl acetate 3:1) gave 3.3g of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester.

To a solution of 4-azido-3-hydroxy-azepane-1-carboxylic acid benzyl ester (3.3g, 11.37mmol) in methanol (50mL) was added triethylamine (5mL) and 1,3-propanedithiol (3.42mL, 35mmol). The mixture was stirred at ambient temperature until TLC analysis showed complete consumption of the starting material. A white precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was triturated with a 1:1 hexane/diethylether mixture to remove excess dithiol and dried under vacuum.
Crude 4-amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (150mg, 0.57mmol), morpholine-4-carboxylic acid 1-carboxy-3,3-dimethyl-butyl ester (120mg, 0.46mmol), EDC (400mg, 2.1mmol), and HOBt (400mg, 2.5mmol) were combined. Dichloromethane (5mL) was added and then 4-methylmorpholine (0.5mL). The mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL) the solution was washed with 1N HCl, sat. aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and evaporated under vacuum. The residue was dissolved in DMSO (5mL). Triethylamine (0.3mL) and then SO_3 pyridine complex (150mg) were added and the mixture was stirred at ambient temperature for 2h. After dilution with ethyl acetate (100mL), the solution was washed with water (50mL) and brine, dried with $MgSO_4$ and evaporated under vacuum. The residue was purified by flash chromatography on silica gel and gave <u>4-[4,4-Dimethyl-2-(morpholine-4-carbonyloxy)-pentanoylamino]-3-oxo-azepane-1-carboxylic acid benzyl e</u>ster (95mg, 0.189mmol) as a white solid.
2:1 mixture of diastereomers, ^1H NMR: (DMSO) 8.14-8.08 (m, 1H), 7.40-7.25 (m, 5H), 5.18-4.89 (m, 3H), 4.51-4.33 (m, 2H), 4.01-3.76 (m, 2H), 3.60-3.25 (m, 8H), 2.95-2.79 (m, 1H), 1.84-1.54 (m, 6H), 0.92/0.91 (s, 9H). MS: $(M+H)^+$ 504. LC/MS m/z=474(M+H)

EXAMPLE 26

(a) <u>(R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide</u>

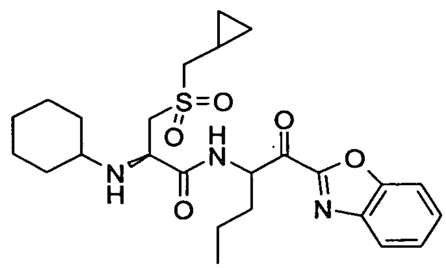


Step 1. (R)-2-Amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-propionamide {90mg, 0.22mmol, Reference Example 11(f)} was dissolved in 5% acetic acid in acetonitrile (10ml). Tetrahydro-4H-pyran-4-one (110mg, 1.1mmol) was added, followed by (polystyrylmethyl)trimethylammonium cyanoborohydride (107mg, 1.1mmol). The resulting reaction mixture was stirred for four hours and then filtered under suction. The solvents were evaporated under high vacuum. The residue was dissolved in 5ml dichloromethane, Silicycle Triamine (940mg, 2.2mmol) was added and the reaction mixture stirred for four hours. It was filtered under suction and the filtrate concentrated under reduced pressure to give <u>(R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide</u> (89mg, 0.18mmol, 82%).

Step 2. (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (89mg, 0.18mmol) was dissolved in 10ml dichloromethane. The Dess-Martin-periodinane (153mg, 0.36mmol) was added and the resulting reaction mixture stirred for two hours. The reaction mixture was poured into a 1/1-mixture of saturated sodium bicarbonate solution and saturated sodium thiosulfate solution. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated sodium bicarbonate solution and brine. The organic phase was dried with magnesium sulfate and the dichloromethane evaporated under reduced pressure. The crude product was purified via flash chromatography (heptane/ethyl acetate 1/1 to elute) to give <u>(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide</u> (24mg, 0.049mmol, 27%). ^{1}H NMR ($CDCl_3$, 300MHz): 8.29 (d, J=8.5Hz, 1H), 7.93 (d, J=8Hz, 1H), 7.68 (d, J=8Hz, 1H), 7.59-7.46 (m, 2H), 5.67 (m, 1H), 3.99-3.93 (m, 2H), 3.84 (dd, J=9.5Hz, 2.5Hz, 1H), 3.56 (dd, J=14.5Hz, 2.5Hz, 1H), 3.42-3.33 (m, 2H), 3.24 (dd, J=14.5Hz, 9.5Hz,

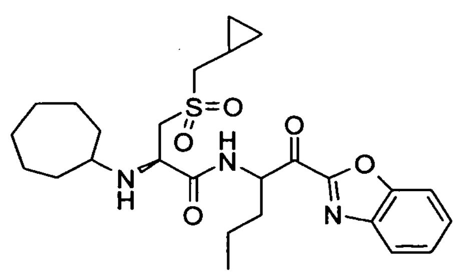
1H), 3.02-2.99 (m, 2H), 2.78-2.71 (m, 1H), 2.13-2.07 (m, 1H), 1.95-1.78 (m, 3H), 1.55-1.41 (m, 5H), 1.23-1.16 (m, 1H), 1.00 (t, J=7.5Hz, 3H), 0.81-0.74 (m, 2H), 0.48-0.43 (m, 2H). LC/MS m/z=492 (M+H)

(b) <u>(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide</u>



By proceeding in a similar manner to Example 26(a) but using cyclohexanone there was prepared <u>(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-cyclopropylmethanesulfonyl-propionamide</u> (predominantly as one diastereomer). ^{1}H NMR ($CDCl_3$, 300MHz): 8.37 (d, J=8.5Hz, 1H), 7.92 (d, J=8Hz, 1H), 7.67 (d, J=8Hz, 1H), 7.59-7.36 (m, 2H), 5.65 (m, 1H), 3.79 (dd, J=9.5Hz, 2.5Hz, 1H), 3.54 (dd, J=14.25Hz, 2.5Hz, 1H), 3.24 (dd, J=14.25Hz, 9.5Hz, 1H), 3.02-2.95 (m, 2H), 2.49 (m, 1H), 2.12-2.07 (m, 1H), 1.96-1.17 (m, 15H), 0.98 (t, J=7Hz, 3H), 0.80-0.72 (m, 2H), 0.48-0.43 (m, 2H). LC/MS m/z=490 (M+H)

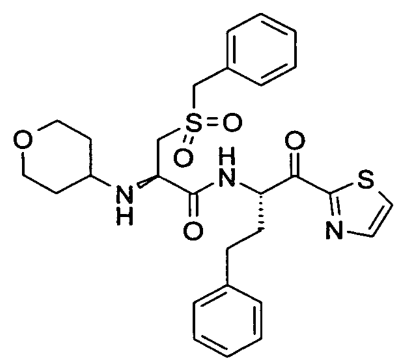
(c) <u>(R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide</u>



By proceeding in a similar manner to Example 26(a) but using cycloheptanone there was prepared <u>(R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-cycloheptylamino-3-cyclopropylmethanesulfonyl-propionamide</u> ^{1}H NMR ($CDCl_3$, 300MHz): [8.36 (d, J=8.5Hz), 8.28 (d, J=8.5Hz), 1H], [8.05 (dd, J=8Hz, 1Hz), 7.97 (dd, J=8.5Hz, 1.5Hz), 1H], [7.92 (d, J=8.5Hz), 7.67 (d, J=8Hz), 1H], 7.59-7.48 (m, 1H), [7.44 (ddd, J=8Hz, 7.5Hz, 1Hz), 7.19

(ddd, J=8Hz, 7.5Hz, 1Hz), 1H], [5.65 (m), 5.62 (m), 1H], [3.82 (dd, J=10Hz, 3Hz), 3.75 (dd, J=9Hz, 3Hz), 1H], [3.55 (dd, J=14.5Hz, 3Hz), 3.49 (dd, J=14.5Hz, 3Hz), 1H], 3.27 (dd, J=14.5Hz, 9Hz, 1H), 3.03-2.96 (m, 2H), 2.72 (m, 1H), 2.14-2.05 (m, 1H), 1.91-1.39 (m, 16H), 1.23-1.17 (m, 1H), [0.99 (t, J=7.25Hz), 0.98 (t, J=7.25Hz), 1H], 0.79-0.7 (m, 2H), 0.48-0.44 (m, 2H). LC/MS m/z=504 (M+H).

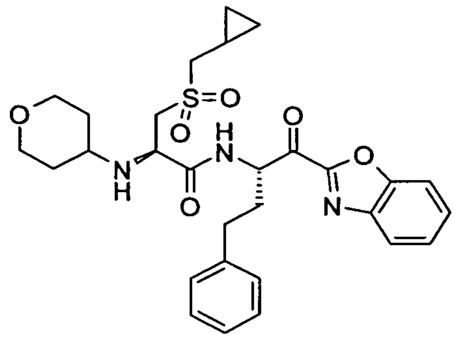
(d) (R)-3-Phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(k)} there was prepared (R)-3-phenylmethanesulfonyl-N-[(S)-3-phenyl-1-(thiazole-2-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide. ^{1}H NMR ($CDCl_3$, 300MHz): 8.27 (d, J=9Hz, 1H), 8.06 (d, J=3Hz, 1H), 7.73 (d, J=3Hz, 1H), 7.47-7.39 (m, 5H), 7.25-7.11 (m, 5H), 5.72 (m, 1H), 4.36 (d, J=14Hz, 1H), 4.31 (d, J=14Hz, 1H), 3.97-3.90 (m, 2H), 3.76 (dd, J=9.5Hz, 3Hz, 1H), 3.40-3.31 (m, 3H), 3.01 (dd, J=14.5Hz, 9.5Hz, 1H), 2.76-2.62 (m, 3H), 2.51-2.40 (m, 1H), 2.22-2.09 (m, 1H), 1.87-1.75 (m, 2H), 1.53-1.38 (m, 3H)

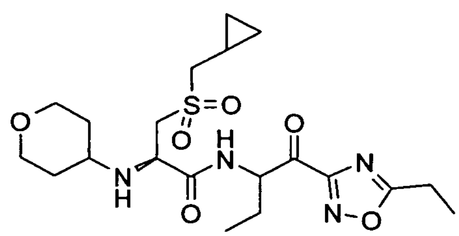
LC/MS m/z=556 (M+H);

(e) (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 26(a) but using (R)-2-amino-N-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(j)} there was prepared (R)-N-[(S)-1-(Benzoxazole-2-carbonyl)-3-phenyl-propyl]-3-cyclopropylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide. ^{1}H NMR ($CDCl_3$, 300MHz): 8.36 (d, J=8.5Hz, 1H), 7.92 (d, J=8Hz, 1H), 7.67 (d, J=8Hz, 1H), 7.60-7.46 (m, 2H), 7.25-7.16 (m, 5H), 5.72 (m, 1H), 3.99-3.93 (m, 2H), 3.81 (dd, J=9.5Hz, 3Hz, 1H), 3.52 (dd, J=14Hz, 3Hz, 1H), 3.41-3.33 (m, 2H), 3.15 (dd, J=14Hz, 9.5Hz, 1H), 3.01-2.70 (m, 2H), 2.81-2.70 (m, 3H), 2.53 (m, 1H), 2.27-2.23 (m, 1H), 1.94-1.44 (m, 5H), 1.22-1.17 (m, 1H), 0.80-0.74 (m, 2H), 0.47-0.42 (m, 2H). LC/MS m/z=554 (M+H);

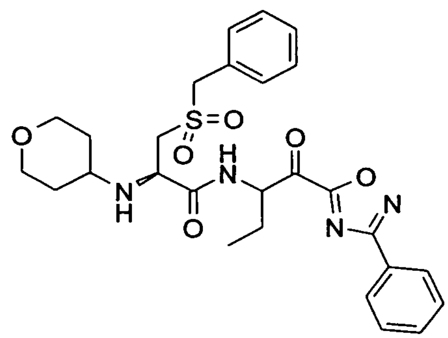
(f) (R)-3-Cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-3-cyclopropylmethanesulfonyl-N-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-propionamide {Reference Example 11(h)} there was prepared (R)-3-cyclopropylmethanesulfonyl-N-[1-(5-ethyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide. ^{1}H NMR ($CDCl_3$, 300MHz): [8.28 (d, J=8.5Hz), 8.15 (d, J=8Hz), 1H], [5.40 (m), 5.33 (m), 1H], 3.99-3.95 (m, 2H), [3.90 (dd, J=10Hz, 3Hz), 3.84 (dd, J=9.5Hz, 3Hz), 1H], [3.55 (dd, J=14Hz, 3Hz), 3.47 (dd, J=14hz, 11Hz), 1H], 3.45-3.33 (m, 2H), 3.23 (dd, 14Hz, 10Hz, 1H), 3.07-2.94 (m, 4H), 2.82-2.71 (m, 1H), 2.19-2.08 (m, 1H), 1.95-1.77 (m, 5H), 1.58-1.43 (m, 1H), 1.45 (t, J=7.5Hz, 3H), 1.23-1.14 (m, 1H), [1.00 (t,

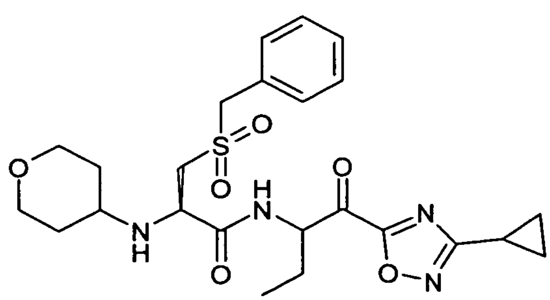
J=7.5Hz), 0.97 (t, J= 7.5Hz), 3H], 0.81-0.73 (m, 2H), 0.48-0.41 (m, 2H). LC/MS m/z=457 (M+H);

(g) (R)-3-Phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-N-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-3-phenylmethanesulfonyl-propionamide {Reference Example 11(g)} there was prepared (R)-3-phenylmethanesulfonyl-N-[1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-2-(tetrahydro-pyran-4-ylamino)-propionamide. ^{1}H NMR ($CDCl_3$, 300MHz): [8.15 (d, J=8Hz), 8.14 (d, J=8Hz), 1H], 7.61-7.39 (m, 10H), [5.46 (m), 5.40 (m), 1H], 4.34-4.28 (m, 2H), 4.09-3.93 (m, 2H), [3.87 (dd, J=9.5Hz, 3Hz), 3.81 (dd, J=9.5Hz, 3Hz), 1H], 3.41-3.32 (m, 3H), [3.16 (dd, J=13.5Hz, 10Hz), 3.11 (dd, J=14Hz, 9.5Hz), 1H], 2.75-2.68 (m, 1H), 2.23-2.13 (m, 1H), 1.96-1.43 (m, 6H), 1.06-0.99 (m, 3H), LC/MS m/z=541 (M+H).

(h) (R)-N-[1-(3-Cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide

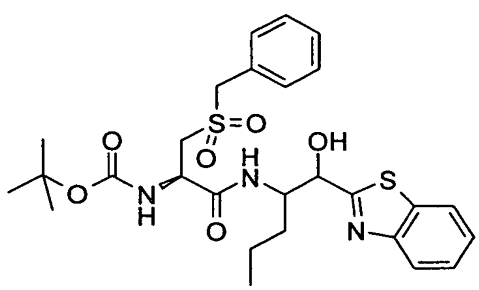


By proceeding in a similar manner to Example 26(a) but using (R)-2-Amino-3-phenylmethanesulfonyl-N-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propyl}-propionamide {Reference Example 11(l)} there was prepared (R)-N-[1-(3-

cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide. ^{1}H NMR ($CDCl_3$, 300MHz): [8.19 (d, J=8.5Hz), 8.11 (d, J=7.5Hz), 1H], 7.46-7.40 (m, 5H), [5.33 (m), 5.27 (m), 1H], 4.55-4.35 (m, 2H), 3.99-3.95 (m, 2H), [3.88 (dd, J=10Hz, 3Hz), 3.83 (dd, J=9.5Hz,3Hz), 1H], 3.44-3.34 (m, 3H), 3.18-3.07 (m, 1H), 2.78-2.67 (m, 1H), 2.24-2.17 (m, 1H), 2.15-2.08 (m, 1H), 1.89-1.72 (m, 3H), 1.55-1.43 (m, 2H), 1.20-1.11 (m, 4H), [0.98 (t, J=7.5Hz), 0.97 (t, J=7.5Hz), 3H]. LC/MS m/z=505 (M+H).

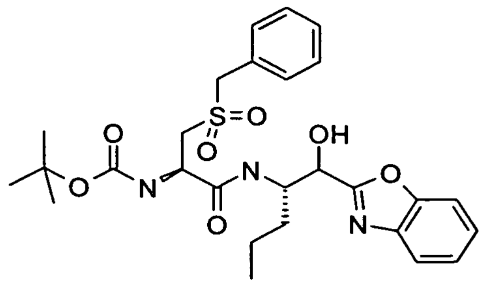
EXAMPLE 27

(a) {(R)-1-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



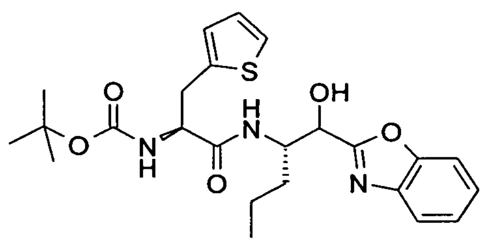
N-cyclohexylcarbodiimide, N'-methyl polystyrene (1.74g, 3.4mmol) suspended in a mixture of dichloromethane (10ml) and dimethylformamide (2mL) was treated with hydroxybenzotriazole (391mg, 2.89mmol) and L-N-boc-benzylsulfonylalanine (876mg, 2.55mmol). This mixture was stirred at room temperature for 30 minutes, then treated with 2-amino-1-benzothiazol-2-yl-pentan-1-ol {400mg, 1.7mmol, Reference Example 17(d)}) and after stirring for a further 2 hours the mixture was then treated with Silicycle-Triamine (2.36g, 8.5mmol). The reaction mixture was stirred for 2 hours and then filtered. The filtrate was evaporated to give the title compound (888mg, 93%). LC/MS m/z=562.

(b) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



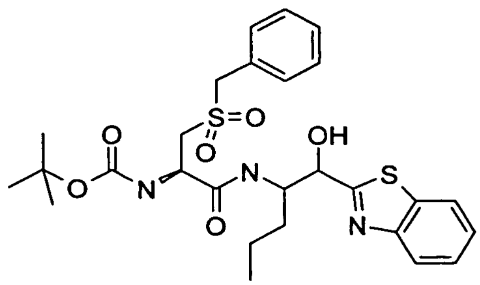
By proceeding in a manner similar to Example 27(a) above but using L-N-boc-benylsulfonylalanine (876mg, 2.55mmol) and (2S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol {374mg, 1.7mmol, Reference Example 17(c)} there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester (908mg, 98%).

(c) {(S)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester



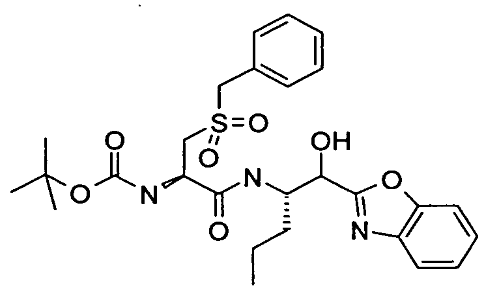
By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (1.76g, 3.4mmol) suspended in dichloromethane (10mL), hydroxybenzotriazole (391mg, 2.89mmol), (2S)- 2-tert-butoxycarbonylamino-3-thiophen-2-yl- propionic acid (692mg, 2.55mmol), (2S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol {374mg, 1.7mmol, Reference Example 17(c)} and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {(S)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-thiophen-2-yl-ethyl}-carbamic acid tert-butyl ester (790mg (1.67mmol, 98%). LC/MS:m/z=562 (M+H).

(d) {(R)-1-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



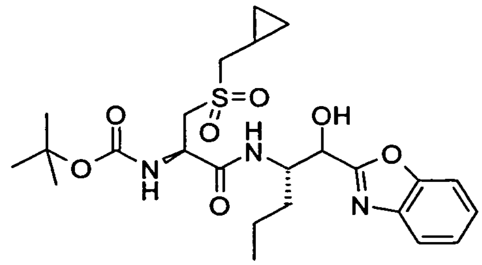
By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (741mg, 1.26mmol), hydroxybenzotriazole (144mg, 1.07mmol), L-N-boc-benzylsulfonylalanine (326mg, 0.95mmol), 2-amino-1-benzothiazol-2-yl-pentan-1-ol {150mg, 0.63mmol, Reference Example 17(d)} and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {(R)-1-[1-(benzothiazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester, LC/MS m/z=562 (M+H), which was used without further purification

(e) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



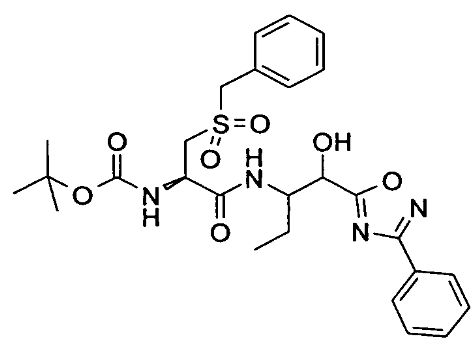
By proceeding in a manner similar to Example 27(a) above but using Resin-bound diimide (1.76g, 3.4mmol), hydroxybenzotriazole (391mg, 2.89mmol), L-N-boc-benzylsulfonylalanine (876mg, 2.55mmol), (2S)-2-amino-1-benzooxazol-2-yl-pentan-1-ol {374mg, 1.7mmol, Reference Example 17(c)} and Silicycle-Triamine (2.36g, 8.5mmol) there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester, LC/MS m/z=546 (M+H), 490 (M=H-butene), which was used directly in the next reaction.

(f) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



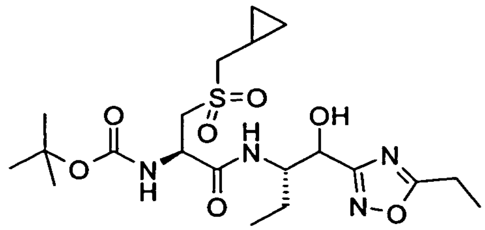
By proceeding in a manner similar to Example 27(a) above but using a suspension of Resin-bound diimide (1.07g, 1.82mmol) in dichloromethane (20ml), hydroxybenzotriazole (209mg, 1.55mmol) and (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (420mg, 1.365mmol, Reference Example 22), (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {200mg 0.91mmol, Reference Example 17(c)} and Silicycle-Triamine (2.8g, 9.1mmol) there was prepared {(R)--1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester (450mg, 97%). LC/MS m/z=532(M+Na), 510 (M+H), 454 (M+H-isobutene).

(g) (R)-1-{1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester



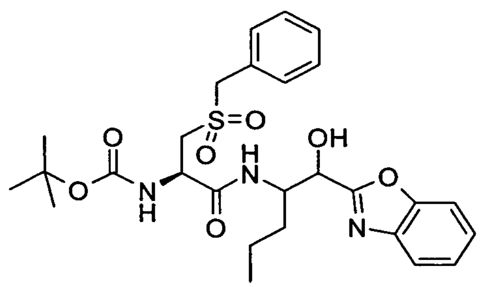
By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (R)-2-tert-butoxycarbonylamino-3-phenylmethanesulfonyl-propionic acid and (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (Reference Example 21) there was prepared (R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester. LC/MS m/z=545(M+Na), 467 (M+H-isobutene), 423 (M+H-Boc).

(i) ((R)-2-Cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester



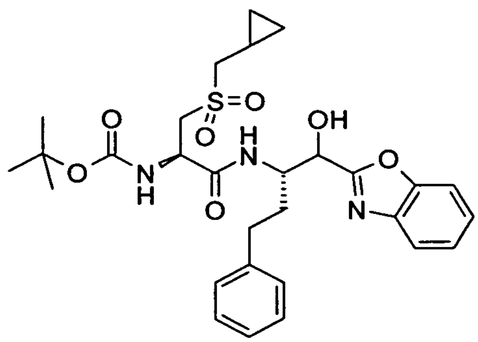
By proceeding in a manner similar to Example 27(f) above but using 2-amino-1-(5-ethyl-[1,2,4]-oxadiazol-3-yl-butan-1-ol (Reference Example 23) there was prepared ((R)-2-cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester. LC/MS m/z=497(M+Na), 419 (M+H-isobutene), 375 (M+H-Boc).

(j) {(R)-1-[1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



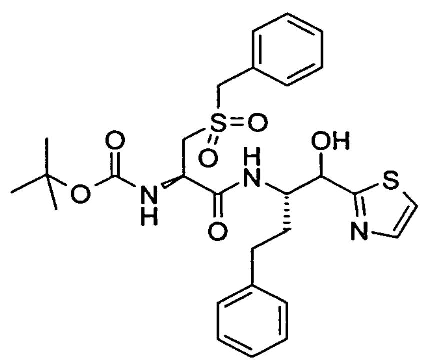
By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {Reference Example 17(c)} there was prepared {(R)-1-[1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=546(M+H), 490 (M+H-isobutene).

(k) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



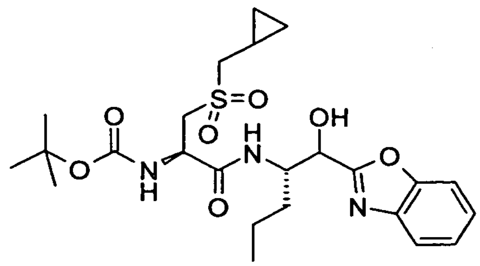
By proceeding in a manner similar to Example 27(f) above but using (2S)-2-amino-4-phenyl-1-benzoxazol-2-yl-butan-1-ol there was prepared {(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=572(M+H), 516 (M+H-isobutene).

(l) {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



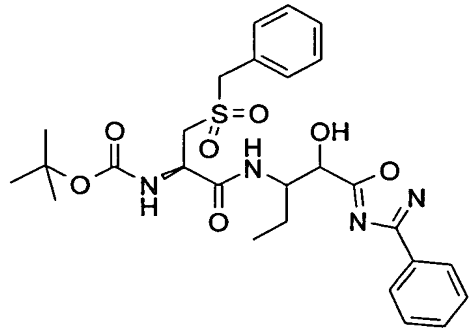
By proceeding in a manner similar to Example 27(f) above but using L-N-boc-benzylsulfonylalanine and (2S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol (Reference Example 13) there was prepared {(R)-1-[(S)-1-(hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=574(M+H).

(m) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



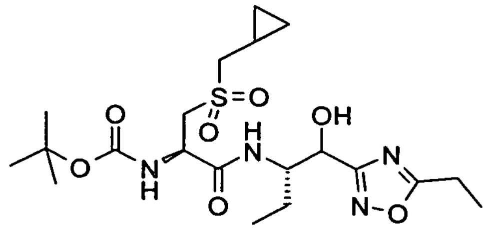
By proceeding in a manner similar to Example 27(f) above but using *N*-Cyclohexylcarbodiimide, *N'*-methyl polystyrene (1.07g, 1.82mmol) suspended in dichloromethane (20mL), hydroxybenzotriazole (209mg, 1.55mmol), (R)-2-tert-butoxycarbonylamino-3-cyclopropylmethanesulfonyl-propionic acid (420mg, 1.365mmol, Reference Example 22), (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {200mg 0.91mmol, Reference Example 17(c)} and Silicycle-Triamine (2.8g, 9.1mmol) there was prepared <u>{(R)-1-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester</u> (450mg, 0.88mmol, 97%). LC/MS m/z=532(M+Na), 510 (M+H), 454 (M+H-isobutene).

(n) <u>(R)-1-{1-[Hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester</u>



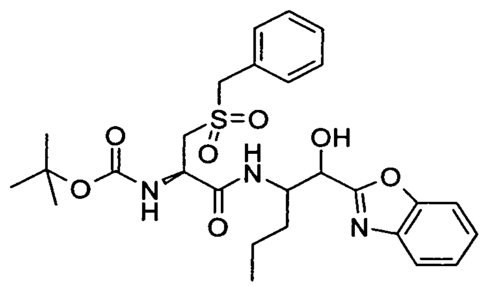
By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-(3-phenyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol (Reference Example 21) there was prepared <u>(R)-1-{1-[hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propylcarbamoyl}-2-phenylmethanesulfonyl-ethyl)-carbamic acid tert-butyl ester</u>. LC/MS m/z=545(M+Na), 467 (M+H-isobutene), 423 (M+H-Boc).

(o) <u>((R)-2-Cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester</u>



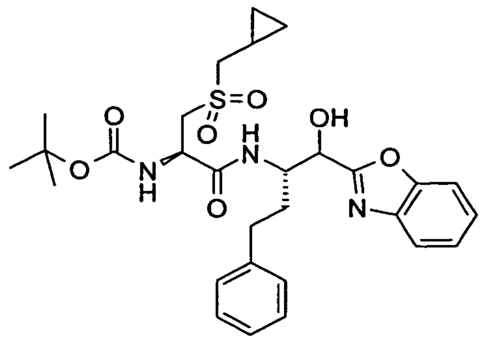
By proceeding in a manner similar to Example 27(m) above but using (S)-2-amino-1-(5-ethyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol there was prepared ((R)-2-Cyclopropylmethanesulfonyl-1-{(S)-1-[(5-ethyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester. LC/MS m/z=497(M+Na), 419 (M+H-isobutene), 375 (M+H-Boc)

(p) {(R)-1-[1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



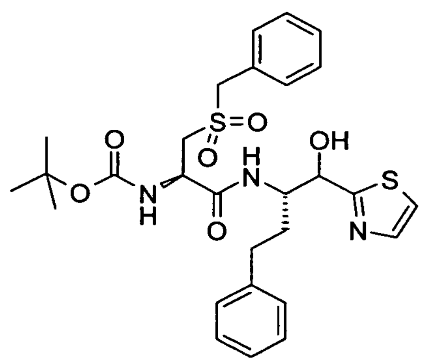
By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol {200mg 0.91mmol, Reference Example 17(c)} there was prepared {(R)-1-[1-(Benzoxazol-2-yl-hydroxy-methyl)-butylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=546(M+H), 490 (M+H-isobutene)

(q) {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



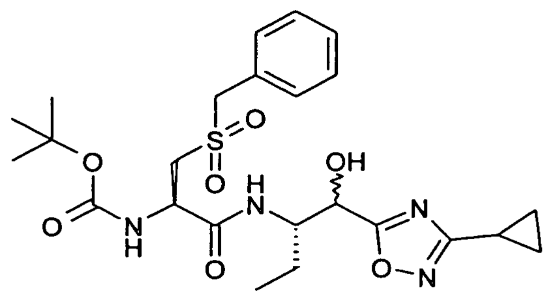
By proceeding in a manner similar to Example 27(m) above but using (2S)-2-amino-4-phenyl-1-benzoxazol-2-yl-butan-1-ol there was prepared {(R)-1-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-3-phenyl-propylcarbamoyl]-2-cyclopropylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=572(M+H), 516 (M+H-isobutene).

(r) {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester



By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (2S)-2-amino-4-phenyl-1-thiazol-2-yl-butan-1-ol (Reference Example 13) there was prepared {(R)-1-[(S)-1-(Hydroxy-thiazol-2-yl-methyl)-3-phenyl-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl}-carbamic acid tert-butyl ester. LC/MS m/z=574(M+H)

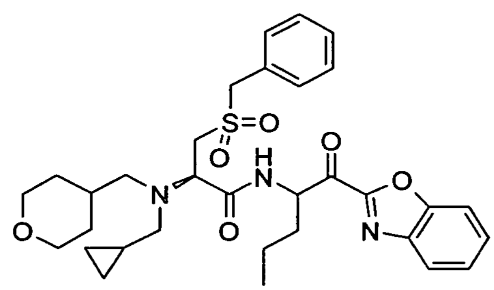
(s) ((R)-2-phenylmethanesulfonyl-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester



By proceeding in a manner similar to Example 27(m) above but using L-N-boc-benzylsulfonylalanine and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (Reference Example 14) there was prepared ((R)-2-phenylmethanesulfonyl-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester.

EXAMPLE 28

(R)-N-[1-(Benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide



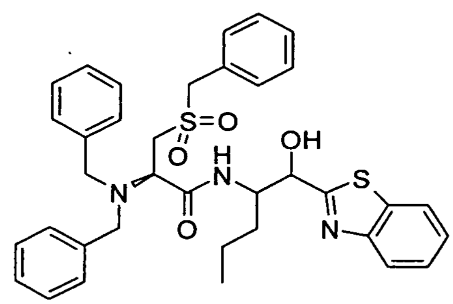
Step 1. (R)-2-Amino-N-[1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {200mg, 0.448mmol, Reference Example 11(i)} was dissolved in 5% acetic acid in acetonitrile (10ml). Tetrahydro-pyran-4-carbaldehyde (51mg, 0.448mmol) was added and the reaction mixture stirred for 16 hours. (Polystyrylmethyl)trimethylammonium cyanoborohydride (218mg, 0.896mmol) was added and the reaction mixture stirred for 3 hours. Cyclopropanecarbaldehyde (157mg, 2.24mmol) was added and stirring continued for 3 hours. The mixture was filtered under suction and the filtrate concentrated under high vacuum.

Step 2. The residue was dissolved in 10ml dichloromethane. The Dess-Martin-periodinane (380mg, 0.896mmol) was added and the resulting reaction mixture stirred for two hours. The reaction mixture was poured into a 1/1-mixture of saturated sodium bicarbonate solution and saturated sodium thiosulfate solution. The aqueous phase was extracted with dichloromethane.

The combined organic phases were washed with saturated sodium bicarbonate solution and brine. The organic phase was dried with magnesium sulfate and the dichloromethane evaporated under reduced pressure. The crude product was purified via flash chromatography (heptane/ethyl acetate 2/1 followed by heptane/ethyl acetate 1/1 to elute) to give R)-N-[1-(benzoxazole-2-carbonyl)-butyl]-2-[cyclopropylmethyl-(tetrahydro-pyran-4-ylmethyl)-amino]-3-phenylmethanesulfonyl-propionamide as mixture of diastereomers. (83mg, 0.139mmol, 31%). LC/MS m/z=596 (M+H) retention time 3.84 (method C).

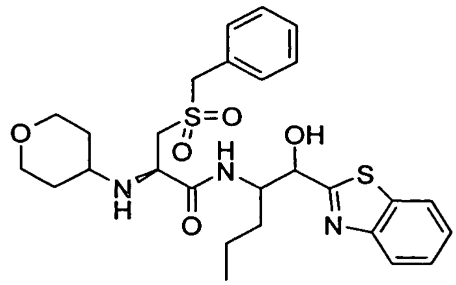
EXAMPLE 29

(a) (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide



(R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {50mg, 0.11mmol, Reference Example 11(a)} was dissolved in a mixture of acetonitrile (5ml) and acetic acid (1ml). Benzaldehyde (56µl, 0.55mmol, 5 equivalents) and resin bound cyanoborohydride (54mg, 0.22mmol, 2 equivalents) were added. The reaction mixture was stirred overnight, filtered under suction and the filtrate evaporated to give the (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide which was used without further purification in the preparation of Example 18(c).

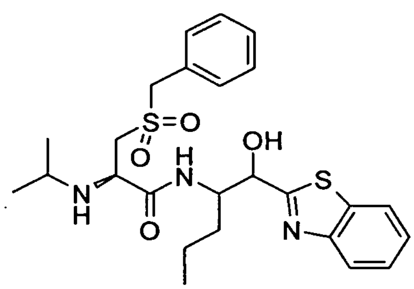
(b) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



By proceeding in a manner similar to Example 29(a) above but using tetrahydro-4H-pyran-4-one (51µl, 0.55mmol, 5 equivalents) there was prepared (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide. LC/MS m/z=546 (M+H)

EXAMPLE 30

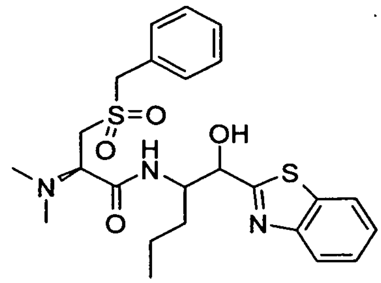
(a) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide



(R)-2-Amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {50mg, 0.11mmol, Reference Example 11(a)} was dissolved in a mixture of acetonitrile (5ml) and acetic acid (1ml). Acetone (500µl) and resin bound cyanoborohydride (54mg, 0.22mmol, 2 equivalents) were added. The reaction mixture was stirred overnight, filtered under suction and concentrated under vacuum. The residue was dissolved in dichloromethane and AP Trisamine (Argonaut Technology) (550mg, 1.2mmol) was added. The mixture was stirred for two hours, filtered under suction and the filtrate concentrated under vacuum to give (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (30mg, 0.06mmol, 54%). LC/MS m/z=504 (M+H).

(b) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-

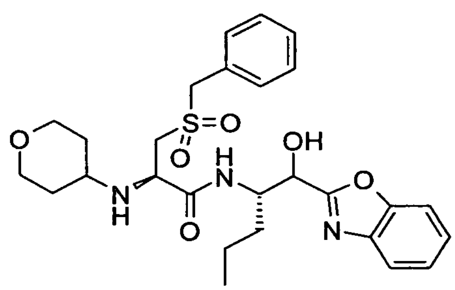
phenylmethanesulfonyl-propionamide



By proceeding in a manner similar to Example 30(a) above but using formaldehyde solution (75μl, 1mmol, 37w-% aqueous solution) there was prepared (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (30mg, 54%). LC/MS m/z=490 (M+H).

EXAMPLE 31

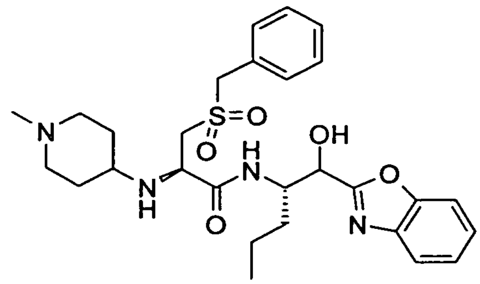
(a) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



A solution of (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {100mg, 0.22mmol, Reference Example 11(c)} in a mixture of acetonitrile (5mL) and acetic acid (1mL) was treated with tetrahydro-4H-pyran-4-one (101μl, 1.1mmol). After agitating at room temperature for 3 hours the mixture was then treated with resin-bound cyanoborohydride (108mg, 0.44mmol) and agitation was continued overnight. The reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane (10mL) and the solution was treated with Silicycle Triamine (611mg, 2.2mmol), then agitated for 2 hours and then filtered. The solution of (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide was used directly in the preparation of Example 20(b).

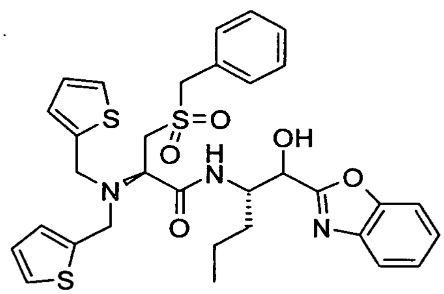
(b) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-

ylamino)-3-phenylmethanesulfonyl-propionamide



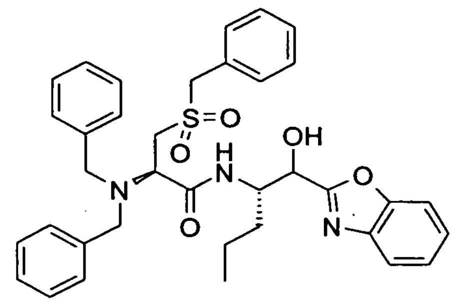
By proceeding in a manner similar to Example 31(a) above but using 1-methyl-4-piperidone (136μl, 1.1mmol) there was prepared (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(1-methyl-piperidin-4-ylamino)-3-phenylmethanesulfonyl-propionamide was used directly in the preparation of Example 19(b).

(c) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide



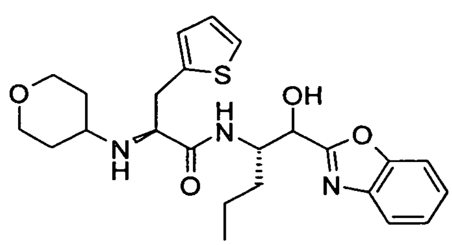
By proceeding in a manner similar to Example 31(a) above but using 2-thiophenecarboxaldehyde (20μl, 0.22mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(bis-thiophen-2-ylmethyl-amino)-3-phenylmethanesulfonyl-propionamide was used directly in the preparation of Example 19(c).

(d) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide



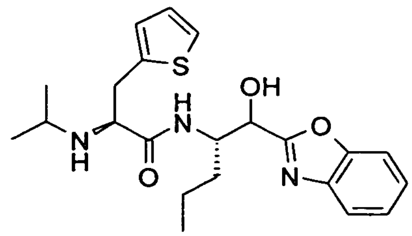
By proceeding in a manner similar to Example 31(a) above but using benzaldehyde (22µl, 0.22mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dibenzylamino-3-phenylmethanesulfonyl-propionamide which was used directly in the preparation of Example 19(d).

(e) (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide



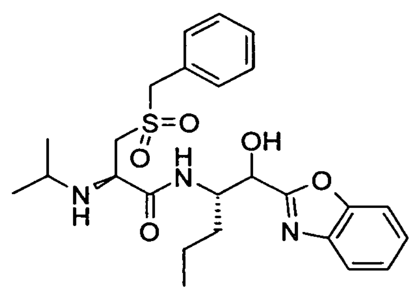
By proceeding in a manner similar to Example 317(a) above but using (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide {82mg, 0.22mmol, Reference Example 11(b)} and tetrahydro-4H-pyran-4-one (101µl, 1.1mmol) there was prepared (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-(tetrahydro-pyran-4-ylamino)-3-thiophen-2-yl-propionamide which was used directly in the preparation of Example 19(e).

(f) (S)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide



By proceeding in a manner similar to Example 31(a) above but using (S)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-thiophen-2-yl-propionamide {82mg, 0.22mmol, Reference Example 11(b)} and acetone (100µl) there was prepared (S)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-thiophen-2-yl-propionamide which was used directly in the preparation of Example 19(f).

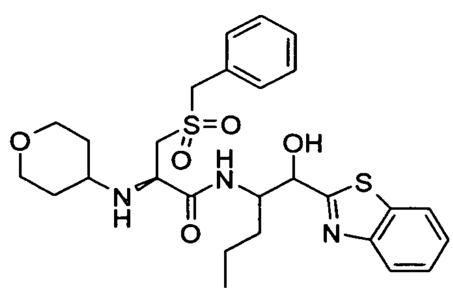
(g) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a manner similar to Example 31(a) above but using acetone (500µl) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl-propionamide (30.5mg, 29%). LC/MS m/z=488 (M+H).

EXAMPLE 32

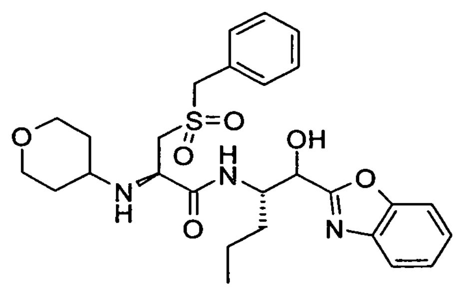
(a) (R)-N-[1-(Benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



A solution of (R)-2-amino-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-

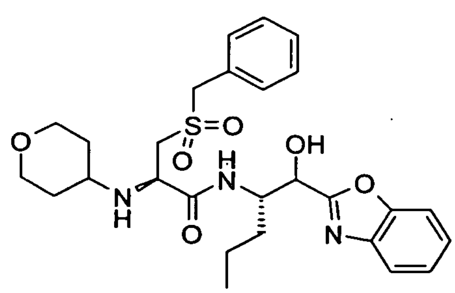
phenylmethanesulfonyl-propionamide {100mg, 0.22mmol, Reference Example 11(a)}in a mixture of acetonitrile and acetic acid (10mL, 95:5, v/v) was treated with tetrahydro-4H-pyran-4-one (101µl, 1.1mmol) and resin-bound cyanoborohydride (108mg, 0.44mmol). This mixture was stirred at room temperature overnight then evaporated. The residue was dissolved in dichloromethane and the solution was treated with Silicycle Triamine (611mg, 2.2mmol) then stirred at room temperature for 2 hours then filtered. The filtrate was evaporated to give (R)-N-[1-(benzothiazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide, LC/MS m/z=546 (M+H), which was used directly in the preparation of Example 18(b).

(b) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



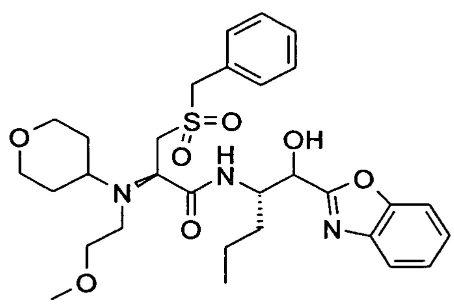
By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {98mg, 0.22mmol, Reference Example 11(c)} there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide, LC/MS m/z=530 (M+H), which was used directly in the preparation of Example 19(a).

(c) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide



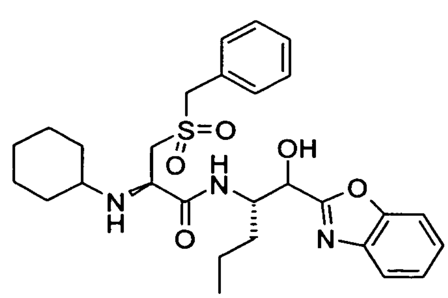
By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {Reference Example 11(c)} there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide (106mg, 91%). LC/MS m/z=530 (M+H).

(d) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide



By proceeding in a manner similar to Example 32(a) above but using (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide {53mg, 0.1mmol, Reference Example32(c)} and 2-methoxyethanal (53mg, 0.55mmol) there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide (56mg, 95%).
LC/MS m/z=588 (M+H)

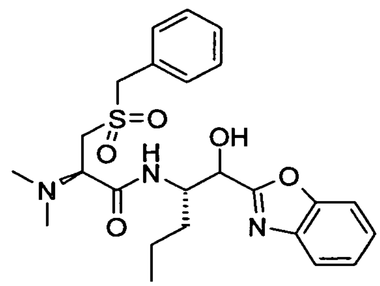
(e) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide



By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {49mg, 0.11mmol, Reference 11(c)} and cyclohexanone (52μl, 0.5mmol) there was prepared (R)-N-

[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide (48mg, 83%).

(f) (R)-N-[(S)-1-(Benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide

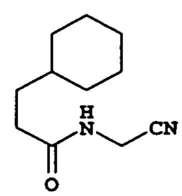


By proceeding in a manner similar to Example 32(a) above but using (R)-2-amino-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-3-phenylmethanesulfonyl-propionamide {49mg, 0.11mmol, Reference Exaple 11(c)} and formaldehyde (75μl, 1mmol, 37 w-% in water), there was prepared (R)-N-[(S)-1-(benzoxazol-2-yl-hydroxy-methyl)-butyl]-2-dimethylamino-3-phenylmethanesulfonyl-propionamide (10mg, 19%). LC/MS m/z=474 (M+H).

EXAMPLE 33

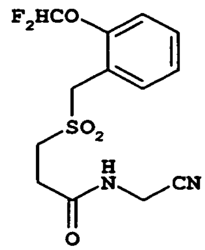
The following compounds of Formula 1 are provided by methods described in the application:

(a) *N*-Cyanomethyl-3-cyclohexyl-propionamide



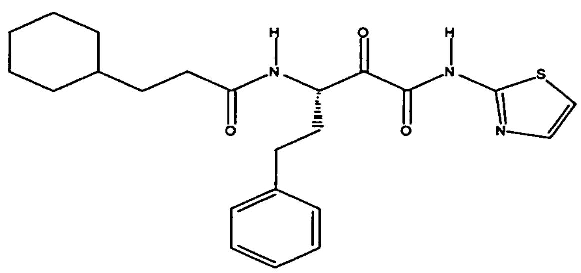
^{1}H NMR: ($CDCl_3$) 6.22 (br s, 1H), 4.20 (s, 2H), 2.23 (m, 2H), 1.65 (m, 5H), 1.50 (m, 2H), 1.10-1.30 (m, 4H), 0.90 (m, 2H); LC-MS: t=3.67min., 193.0(M-1), 195.1(M+1). MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.);

(b) N-Cyanomethyl-3-(2-difluoromethoxy-phenylmethanesulfonyl)-propionamide



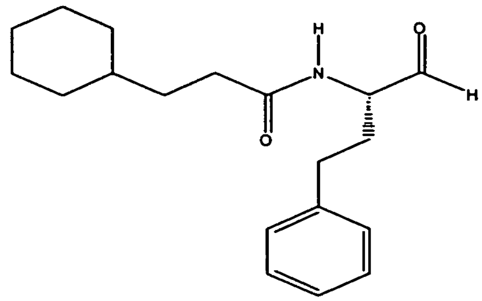
^{1}H NMR: ($CDCl_3$) 7.52 (d, 1H, J=8Hz), 7.43 (t, 1H, J=8Hz), 7.29 (d, 1H, J=8Hz), 7.20 (d, 1H, J=8Hz), 6.40 (m, 1H), 4.41 (s,2H), 4.16 (d, 2H, J=6Hz), 3.72 (s, 1H), 3.34 (t, 2H, J=8Hz), 2.77 (t, 2H, J=8Hz); LC-MS: t=3.02min., 331.1(M-1), 333.1(M+1). MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.).

(c) 3-(3-Cyclohexyl-propionylamino)-2-oxo-5-phenyl-pentanoic acid thiazol-2-ylamide



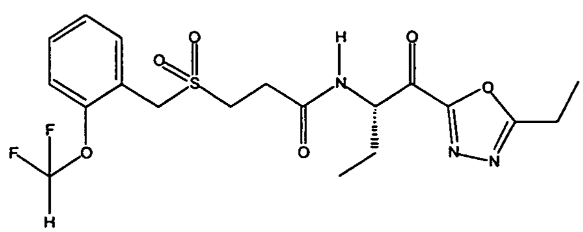
data for the compound as drawn and for it's enol and hydrate forms: LC-MS: t=4.74min. 426.4(M-1), 428.2(M+1); 4.97min, 426.2 (M-1), 428.2 (M+1); 5.57min, 426.3(M-1), 427.9 (M+1). MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% acetonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

(d) 3-Cyclohexyl-N-(1-formyl-3-phenyl-propyl)-propionamide



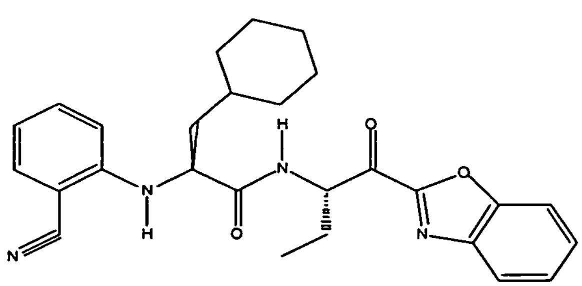
LC-MS: t=4.57min., 300.4(M-1), 302.3(M+1). MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 6min. Then gradient back to 100% A, 0% B from t = 7 to t = 15 min.)

(f) <u>3-(2-Difluoromethoxy-phenylmethanesulfonyl)-*N*-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-propionamide</u>



LC-MS: R_T =2.32min., 460.3(M+1) 482.2(M+23) MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 2.5min. Then gradient back to 100% A, 0% B from t = 3.0 to t = 3.5 min. Then gradient held at 100%A, 0%B from t=3.5 to 5 min.)

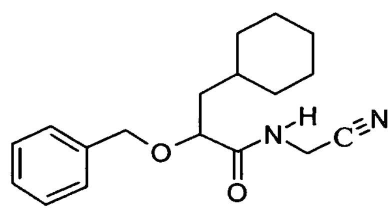
(g) <u>*N*-[(S)-1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-cyano-phenylamino)-3-cyclohexyl-propionamide</u>



^{1}H NMR: ($CDCl_3$) 7.83 (d, 1H, J=8Hz), 7.59 (d, 1H, J=8Hz), 7.43-7.58 (m, 2H), 7.02-7.25(m, 4H), 6.59 (t, 1H, J=8Hz), 6.49 (d,1H,J=8Hz), 5.40-5.47 (m, 1H), 4.77 (m, 1H), 3.83-3.88 (m, 1H), 2.12-2.22 (m, 1H), 1.85-2.00 (m, 2H), 1.55-1.83 (m. 8H), 1.12-1.35 (m,4H), 0.95-1.10 (m, 3H); LC-MS: t=2.97min., 457.5(M-1), 459.3(M+1), 481.4(M+23) MS: API 150EX. (LC: Agilent 1100Series, Column: Phenomenex, 5u ODS3 100A 100X3mm. Flow Rate: 2ml/min. Two solvent gradient: Solvent A, 99% water, 1% acetonitrile, 0.1% AcOH. Solvent B, 99% actonitrile, 1% water, 0.1% AcOH. Gradient from 100% A, 0% B to 0% A, 100% B from t = 0 to t = 2.5min. Then gradient back to 100% A, 0% B from t = 3.0 to t = 3.5 min. Then gradient held at 100%A, 0%B from t=3.5 to 5 min.)

(h) *N*-Cyanomethyl-3-cyclohexyl-2-(4-methoxy-phenoxy)-propionamide (Compound 1); ^{1}H NMR: ($CDCl_3$) 7.42-7.36 (m, 5H), 6.90 (t, 1H), 4.55 (d, 1H), 4.51 (d, 1H), 4.22 (dd, 1H), 4.16 (dd, 1H), 4.00 (t, 1H), 1.70-0.80 (m, 13H); MS: (M^++1) 301;

(i) 2-Benzyloxy-*N*-cyanomethyl-3-cyclohexyl-propionamide (Compound 2)



using 2(R)-benzyloxy-4-phenyl-butyric acid as starting material. ^{1}H NMR: ($CDCl_3$) δ 6.84-6.80 (m, 4H), 6.75 (t, 1H), 4.55 (dd, 1H), 4.24 (dd, 1H), 4.12 (dd, 1H), 3.78 (s, 3H), 1.80-0.85 (m, 13H); MS: (M-1) 315.

(j) (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-benzyloxy-3-phenylmethanesulfonyl-propionamide (Compound 3); ^{1}H NMR: ($CDCl_3$) 7.89 (d, 1H), 7.68 (d, 1H), 7.60-7.32 (m, 13H), 5.70 (m, 1H), 4.79 (d, 1H), 4.77 (d, 1H), 4.53 (dd, 1H), 4.33 (d, 1H), 4.30 (d, 1H), 3.38 (dd, 1H), 3.25 (dd, 1H), 2.15-2.05 (m, 1H), 1.84-75 (m, 1H), 1.45-1.30 (m, 2H), 0.93 (t, 3H); MS: (M^++1) 535, (M-1) 533;

(k) (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-methoxymethoxy-3-phenylmethanesulfonyl-propionamide (Compound 9); ^{1}HNMR (DMSO): 8.87(d, J=6.91Hz, 1H), 7.99(d, J=7.91Hz, 1H), 7.89(d, J=8.15Hz, 1H), 7.64(t, J=8.1Hz, 1H), 7.54(t, J=8.1Hz, 1H), 7.4-7.3(m, 5H), 5.3-5.2(m, 1H), 4.7-4.65(m, 1H), 4.65-4.63(m, 2H), 4.55-4.50(m, 2H),

3.53-3.26(m, 2H), 3.34(s, 3H), 2.11-1.98(m, 1H), 1.81-1.69(m, 1H), 0.97(t, J=7.15Hz, 3H); MS: 473(M-1), 497(M+23);

(l) (*S*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-hydroxy-3-phenyl-propionamide (Compound 10);

(m) (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-phenylmethanesulfonyl-2-triisopropylsilanyloxy-propionamide (Compound 12); ^{1}HNMR (CD_3Cl): 7.93(d, J=8.15Hz, 1H), 7.6(d, J=8.1Hz, 1H), 7.6-7.4(m, 3H), 7.4-7.3(m, 5H), 5.85-5.73(m, 1H), 4.85-4.74(m, 1H), 4.5-4.3(m, 2H), 3.47-3.35(m, 2H), 2.35-2.15(m, 1H), 2.15-1.95(m, 1H), 1.3-0.8(m, 24H); MS: 609.4(M+23);

(n) (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenylmethanesulfonyl-propionamide (Compound 13); ^{1}HNMR (CD_3Cl): 8.21(d, J=8.67Hz, 1H), 7.98(d, J=8.6Hz, 1H), 7.7-7.55(m, 3H), 7.45-7.3(m, 5H), 5.8-5.7(m, 1H), 4.75-4.6(m, 1H), 4.4-4.3(m, 2H), 4.08(br, 1H), 3.62-3.5(m, 1H), 3.3-3.1(m, 1H), 2.3-2.15(m, 1H), 2.05-1.9(m, 1H), 0.997(t, J=7.4Hz, 3H); MS: 469.2(M+23);

(o) (*R*)-2-hydroxy-3-phenylmethanesulfonyl-*N*-[(S)-1-(1-pyridazin-3-yl-methanoyl)-butyl]-propionamide (Compound 16); ^{1}HNMR (CD_3Cl): 9.35(dd, J=4.93Hz, J=1.72Hz, 1H), 8.14(dd, J=1.72Hz, J=8.39Hz, 1H), 7.69(dd, J=4.93Hz, J=8.39Hz, 1H), 7.65(d, J=7.6Hz, 1H), 7.5-7.36(m, 5H), 6.04-5.96(m, 1H), 4.75-4.63(m, 1H), 4.45-4.3(m, 3H), 3.53(dd, J=2.48Hz, J=14.85Hz, 1H), 3.22(dd, J=14.82Hz, J=2.48Hz, 1H), 2.2-2.07(m, 1H), 1.81-1.65(m, 1H), 1.6-1.2(m, 2H), 0.93(t, J=7.18Hz, 3H); MS: 403.6(M-1), 428(M+23);

(p) (*S*)-3-((*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino)-2-oxo-pentanoic acid benzylamide (Compound 18); ^{1}HNMR (CD_3Cl): 7.45-7.25(m, 10H), 5.34-5.26(m, 1H), 4.7-4.6(m, 1H), 4.47(d, J=6.18Hz, 2H), 4.4-4.3(m, 2H), 4.15-4.05(m, 1H), 3.55-3.45(m, 1H), 3.25-3.13(m, 1H), 22.2-2.0(m, 1H), 1.8-1.6(m, 1H), 1.61(s, 2H), 0.95(t, J=6.91Hz, 3H); MS: 469.2(M+23);

(q) (*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 21); ^{1}HNMR (CD_3Cl): 7.91(d,

J=7.91Hz, 1H), 7.75(d, J=7.9Hz, 1H), 7.7-7.2(m, 6H), 6.63(t, J=73.41Hz, 1H), 5.7-5.58(m, 1H), 5.4-5.29(m, 1H), 4.7-4.6(m, 1H), 4.51(s, 2H), 4.19(br, 1H), 3.72-3.63(m, 1H), 3.35-3.2(m, 1H), 2.3-2.0(m, 1H), 2.0-1.7(m, 1H), 0.99(t, J=6.9Hz, 3H); MS: 495.5(M-1), 497.2(M+1);

(r) (*R*)-*N*-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 22); ^{1}HNMR (CD_3Cl): 8.21(d, J=8.15Hz, 1H), 7.99(d, J=8.1Hz, 1H), 7.73-7.2(m, 6H), 6.63(t, J=73.4Hz, 1H), 5.85-5.75(m, 1H), 5.3(s, 1H), 4.78-4.7(m, 1H), 4.56-4.4(m, 2H), 4.19-4.09(m, 1H), 3.7-3.6(m, 1H), 3.35-3.2(m, 1H), 2.28(s, 2H), 1.27(t, J=6.9Hz, 3H); MS; 511.4(M-1), 513.6(M+1); and

(s) (2R,5S)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl]-6-ethoxy-5-ethyl-morpholin-3-one (Compound 24).

ENZYME ASSAY EXAMPLE

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 □L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 □L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 □L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 □L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (□ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

ENZYME ASSAY EXAMPLE

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 □L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 □L, comprising: *N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human

cathepsin B (0.025 pMoles in 25 □L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 □L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (□ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

ENZYME ASSAY EXAMPLE

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 □L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 □L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 □L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 □L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (□ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

ENZYME ASSAY EXAMPLE

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 □L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 □L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 □L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (1 nMoles in 25 □L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (□ 460 nm) for 5 minutes. Apparent

inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

According to applicants' assays conducted as described above, the apparent inhibition constants (K_i) for the following listed compoundsof the invention, against Cathepsin S, were about or below 0.01 □M:

morpholine-4-carboxylic acid (R)-1-(cyanomethyl-carbamoyl)-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 31), Example 3(a);

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 11), Example 4(a);

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 14), Example 4(b);

morpholine-4-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzothiazol-2-yl-methanoyl)-propylcarbamoyl]-2-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-ethyl ester, (Compound 15), Example 4(c);

pyrrolidine-1-carboxylic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 19). Example 4(d);

dimethyl-carbamic acid (*R*)-1-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 20)., Example 4(e);

morpholine-4-carboxylic acid (R)-1-[(S)-1-(1-benzylcarbamoyl-methanoyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, (Compound 25). Example 4(f);

morpholine-4-carboxylic acid (S)-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, Example 4(g);

morpholine-4-carboxylic acid (S)-1-[(S)-1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-2-phenylmethanesulfonyl-ethyl ester, Example 4(h);

(R)-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-*N*-((S)-1-formyl-propyl)-2-hydroxy-propionamide. (Compound 23), Example 6;

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-hydroxy-3-phenyl-methanesulfonyl-propionamide, (Compound 5), Example 7;

(S)-3-{3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-propanoylamino}-2-oxo-pentanoic acid benzylamide, (Compound 27), Example 8(a);

(R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-(2-nitro-phenylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 28), Example 9;

(R)-*N*-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-butyl]-2-(5-nitro-thiazol-2-ylamino)-3-phenylmethanesulfonyl-propionamide, (Compound 29), Example 10;

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-3-phenylmethanesulfonyl-2-(tetrahydro-pyran-4-ylamino)-propionamide; Example 19(a);

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-isopropylamino-3-phenylmethanesulfonyl propionamide, Example 21(a);

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-[(2-methoxy-ethyl)-(tetrahydro-pyran-4-yl)-amino]-3-phenylmethanesulfonyl-propionamide, Example 21(b);

(R)-N-[(S)-1-(benzoxazole-2-carbonyl)-butyl]-2-cyclohexylamino-3-phenylmethanesulfonyl-propionamide, Example 21(c);

morpholine-4-carboxylic acid (S)-2-cyclohexyl-1-[(S)-1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propylcarbamoyl]-ethyl ester, Example 24(b);

3-(2-difluoromethoxy-phenylmethanesulfonyl)-*N*-[(S)-1-(oxazolo[4,5-*b*]pyridine-2-carbonyl)-propyl]-propionamide, Example 33(e);

(*S*)-3-((*R*)-2-hydroxy-3-phenylmethanesulfonyl-propanoylamino)-2-oxo-pentanoic acid benzylamide (Compound 18), Example 33(p);

(*R*)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-3-[2-(1,1-difluoro-methoxy)-phenylmethanesulfonyl]-2-hydroxy-propionamide (Compound 21), Example 33(q);

Moreover, the compounds of the present invention were observed to have varying degrees of selective inhibitory action on cathepsin S protease. For example, the above listed 22 compounds were found to inhibit cathepsin S protease activity at concentrations that are more than 75 fold less than those concentrations required to produce an equiactive inhibition on cathepsin K protease.

EXAMPLE

Representative Pharmaceutical Formulations Containing a Compound of Formula I

ORAL FORMULATION

Compound of Formula I	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

Compound of Formula I	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.